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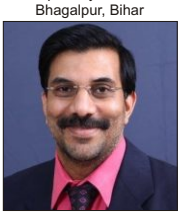
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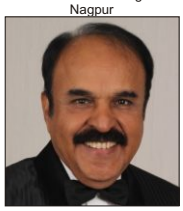
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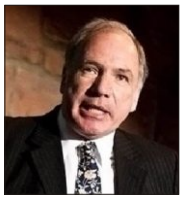
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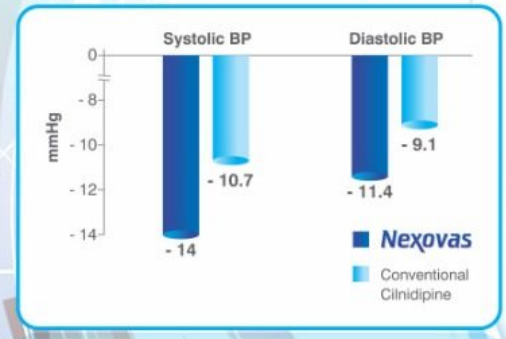

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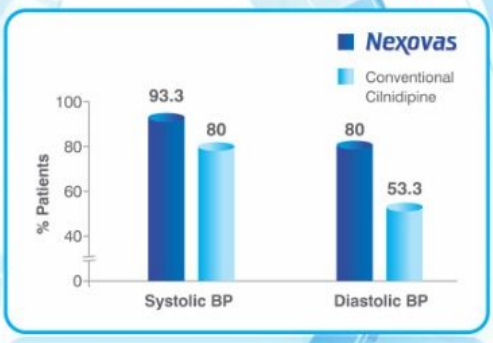

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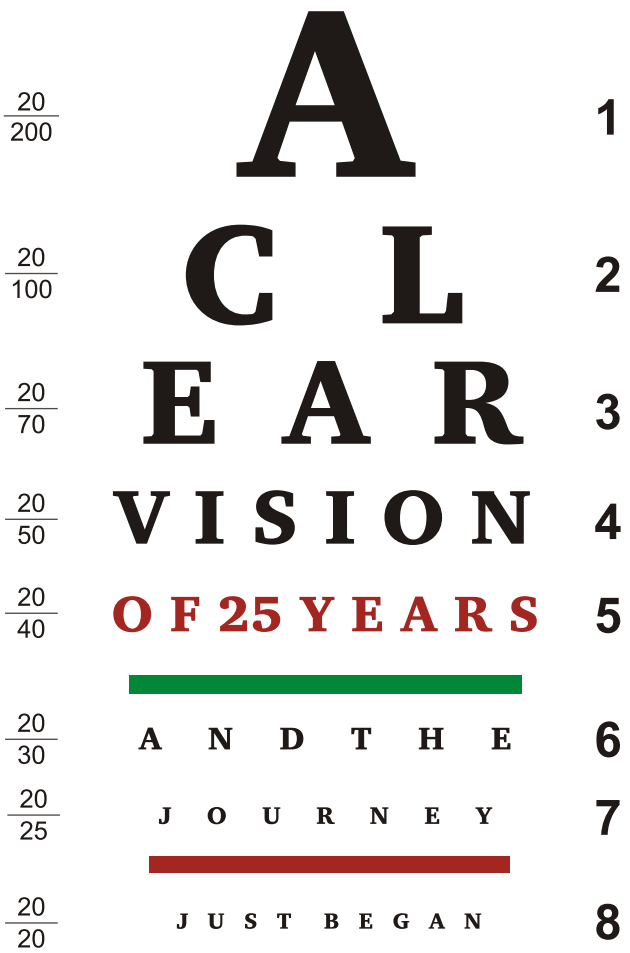

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Contents

(Continued next page)

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Contents

Editorial

Diabetes in India at 75 : Crossroads with History and Future

Introduction : Diabetes is one of the largest global health emergencies of this century, affecting more than half a billion people worldwide[1]. Globally, an estimated 240million people are living with undiagnosed diabetes[1]. Non-Communicable Diseases (NCDs) accounted for 74% of deaths globally in 2019, according to World Health Organization, out of which, diabetes resulted in approximately 1.6 million deaths, therefore becoming the ninth leading cause of death globally[2].

Type 2 Diabetes (T2D), previously considered a disease of affluent "Western" countries has now spread globally, accounting for about 90% of all diabetes cases. T2D is a major cause of disability and death affecting across all age groups. The number of children and adolescents living with diabetes is increasing annually. In 2021, over 1.2 million children and adolescents have been diagnosed with type 1 diabetes. Majority of type 1 diabetes children in India are from a poor socioeconomic background and comprehensive diagnostic, treatment and team based facilities are sparcely available. There is a huge economic burden due to direct health expenditures from diabetes, nearly about one trillion USD[1].

Global burden : Worldwide, an estimated 537 million adults in the age group of 20–79 years(about 10.5% of all adults) have diabetes. By 2030, 643 million and by 2045, 783 million adults (aged 20–79 years) are projected to be living with diabetes. Thus, diabetes is estimated to increase by 46%, while the world's population is estimated to grow by 20%[1].

Burden of Diabetes in India: 74.2 million people live with diabetes in India in 2021 and by 2045 the count is expected to rise to 124.9 million, with estimated 53.1% having undiagnosed diabetes[1]. This has led to a significant increase in mortality due to NCDs.

The prevalence of diabetes in India has risen from 7.1% in 2009 to 8.9% in 2019[3]. Indian Council of Medical Research INDIAB Study on diabetes and prediabetes comprising of data from 15 states / UT, the largest epidemiological, population-based survey conducted at National Level, highlighted the prevalence of diabetes ranging between 3.5 - 8.7% in rural and 5.8 - 15.5% in urban areas. Diabetes prevalence was higher in urban areas (11.2%) compared to that of rural areas (5.2%). The prevalence of prediabetes ranged from 5.8- 14.7% in rural to 7.2-16.2% in urban areas with higher prevalence of prediabetes compared to diabetes in most states, indicating presence of large number of individuals at high risk of developing T2D in near future. Prediabetic Asian Indians progress more rapidly to overt T2D compared to other ethnic groups[4].

Moreover the phase 2 of INDIAB Study suggested that achievement of treatment targets like glycaemic control, lipid and blood pressure control remain suboptimal in Indian diabetes subjects[5].

Combined efforts of both academic and translational science are needed to improve the quality of life and better life expectancy for people with diabetes[6]. The year 2021 marked 100 years of insulin discovery in Toronto in 1921, which brought hope for the first time to people with type 1 diabetes and lead to a Nobel Prize in 1923[6]. Over the years, there has been innovations in the scientific journey of diabetes medications including insulin[7]. Timely insulin initiation may generate a good metabolic memory, reducing chronic complications, but is an important challenge in India[8]. Timely insulin initiation therapy leads to improved beta- cell function and mass by inducing 'beta-cell rest'[9]. The spurt in childhood obesity worldwide and specially in India, has triggered the dramatic rise of T2DM in young in India in recent years[10]. This is linked to the global economic growth and changes in lifestyle and dietery habits. T2DM in childhood can be contained to a large extent through lifestyle modification measures. School based interventions like nutrition and physical education and regular health checkup are essential for prevention of T2DM in children and management of T1DM.

As we look at the future, we see new diabetes treatment and technologies device innovations that will bring greater flexibility and a more holistic approach to diabetes care. Once-weekly dosage of basal insulins, glucose-sensitive and cardio-protective insulins, next generation oral treatments, other innovative approaches such as new digital health solutions, transformational stem-cell therapies and even the hope for curative treatment someday are all going to be a part of our effort to defeat diabetes[7].

In conclusion, our task is cut out, we need a clear population strategy to detect diabetes at an early stage and initiate action to prevent complications, as almost one in two adults with diabetes are unaware that they have the condition. It is quintessential to improve the mass healthcare delivery system and quality of care to support diabetes subjects beyond diagnosis with multifaceted treatment for early and persistant glycemic, lipid and blood pressure control to prevention complications. Insulin therapy is an important component of treatment of diabetes. Concerted effort, to strengthen and empower the public health sector, in health promotion, diabetes screening, prevention and management, will go a long way in reducing the impact of diabetes.

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Original Article

Electrocardiographic Manifestations in COVID-19 Patients — An Observational Study from a Tertiary Care Centre in North Eastern India

Manish Kapoor[1], Arun Kumar[2], Tony Ete[3], Star Pala[4], Vanlalmalsawmdangliana[5], Rinchin Dorjee Megeji[6], Taso Beyong[7]

Introduction : The Coronavirus disease 2019 (COVID-19) primarily involves respiratory system but may also affect the Cardiovascular System leading to abnormal ECGs. Its early recognition is crucial as it may be associated with increased mortality. Hence we aimed to find out various Electrocardiographic (ECG) manifestations of COVID-19 patients admitted in a Tertiary Care Hospital and its relation to disease severity.

Methods : We performed a hospital-based retrospective observational study between April, 2021 to November 2021 and analyzed the ECG changes at admission by three Cardiologists according to standard definitions and diagnostic criteria.

Results : Out of 579 patients, ECG of 473 was available for analysis. ECG was normal in 227 (48%) and abnormal in 246 (52%) patients. Most common abnormal ECG finding in COVID19 patients was Sinus Tachycardia(19.5%) and less common findings were Sinus Bradycardia (5.3%), Incomplete Right Bundle Branch Block (RBBB) (3.2%), atrial fibrillation (2.5%), complete RBBB (2.3%), atrial premature complexes (2.3%), S1Q1T3 pattern (2.1%), first degree AV block (1.5%), ST-T wave changes (1.3%), Atrial flutter (1.1%). In mechanically ventilated patients, incidence of acute Right Ventricular Pressure Overload (RVPO) related ECG findings were more frequent.

Conclusion : There is a wide spectrum of ECG manifestations in COVID-19 patients which varies depending upon the severity of COVID as well as prior Cardiovascular status, associated comorbidities and need for ventilatory support. Knowledge of ECG changes might help in risk stratification and triaging of COVID-19 patients.

[*J Indian Med Assoc* 2022; **120(8):** 12-6]

Key words **: COVID-19 India, 12 lead ECG, COVID severity, Medical Comorbidities, Tertiary Care Centre.**

COVID-19 pandemic started after the outburst from Wuhan, China in December 2019 and has spread across the whole World since. As of now, it has affected more than 200 Countries and 4.3 million deaths Globally. An early study from China indicated that 16.7% of hospitalized and 44.4% of ICU patients with COVID-19 had arrhythmias[1]. In addition, the SARS-CoV-2 virus has a specific predilection over Angiotensin-converting receptor-2 (ACE2)[2], a receptor that is the predominant receptor in the Cardiovascular System and the patients with comorbidities had a higher risk of severe cardiac injury[3,4]. As the pandemic continues to rage, wide variety of Arrhythmias, its mechanisms related to direct cardiac injury, hypoxia,

Editor's Comment :

- COVID-19 has affected millions of lives across the Globe. Many patients hospitalized with COVID-19 infection have developed cardiac abnormalities and related ECG changes. Identifying ECG patterns that might be related to COVID-19 is vital. This study tried to find out relevant ECG findings associated with COVID-19 and to correlate these Electrocardiographic abnormalities with their severity. Most common finding was sinus tachycardia but others included SVTs such as atrial fibrillation or flutter, ventricular arrhythmias such as VT or VF, bradycardia, interval and axis changes (QT prolongation) and ST-segment and T wave changes. Knowledge of these findings may assist clinicians in the evaluation, management and prognostication of COVID-19 infected patients. Larger studies comparing pre, post and follow-up ECGs of COVID-19 infected patients are needed for better management and treatment outcomes.

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electrolyte imbalance, endothelial injury and interaction with therapeutics (hydroxychloroquine, azithromycin) were identified[5]. It has also been reported that the incidence of cardiac arrest during hospital stay increased during this pandemic[6]. Data from earlier studies suggested that 27.8% of in-hospital COVID-19 patients had myocardial injury indicated by troponin elevation and a higher incidence of Malignant Arrhythmias[7]. So the identification of Electrocardiographic findings at the time of admission and during an in-hospital stay of COVID-19 patients may help in early risk stratification and management. The Heart Rhythm Society (HRS), American College of Cardiology (ACC) and the American Heart Association (AHA) released a joint statement with recommendations regarding exposure risks, triage, cardiac arrhythmias as well as how to manage electrophysiology procedures, clinic visits, and device interrogations during this pandemic[8]. Here we aimed to find out various Electrocardiographic (ECG) manifestations of COVID-19 patients and their relation to disease severity admitted in a Tertiary Care Hospital in North Eastern India.

Materials and Methods

A hospital-based retrospective observational study was carried out in the period between April, 2021 to November, 2021. The project was approved by the Institutional Scientific Advisory Committee as well as the Institutional Ethics Committee. The study protocol was approved by the Clinical Trial Screening and the Ethics Committee of the hospital. We assessed the ECG findings during admission and the severity of COVID-19, associated comorbid conditions were analyzed. Out of 579 patients admitted during that period only 473 patients had ECG. The inclusion criteria were age >18 years, positive for SARS-CoV2 infection, those patients had ECG at the time of admission. The exclusion criteria were pregnant patients, uncertain COVID-19 infection and unavailability of ECG. ECG analysis was independently performed by three Experienced Cardiologists according to standard definitions and diagnostic criteria according to Chou's Book of Electrocardiography[9]. According to our institutional protocol COVID-19 patients were classified into four categories namely (i) Category A- asymptomatic, (ii) Category B- symptomatic not requiring oxygen support, (iii) Category C-symptomatic requiring oxygen support, (iv) Category D-symptomatic requireng ventilator support.

Statistical analysis :

Descriptive analysis was used to describe the Socio-demographic characteristics of the study participants in frequency and percentage. Continuous variables were expressed as mean and standard deviation. Percentages were used for categorical variables. Statistical significance was defined as a p-value less than 0.05. Data entry and statistical analysis were done on SSPS version 23.0. A comparison was performed with a chi-square test between categorical variables.

Total patients-579 positive for SARS-COV-2 infection

Results

Inclusion criteria :

>18 years, ECG available

Exclusion criteria :

Pregnant women, ECG unavailability

473 patients ECG -analysed

Out of 579 patients admitted during this period, 473 patients' ECG was available (Fig 1). Among them,

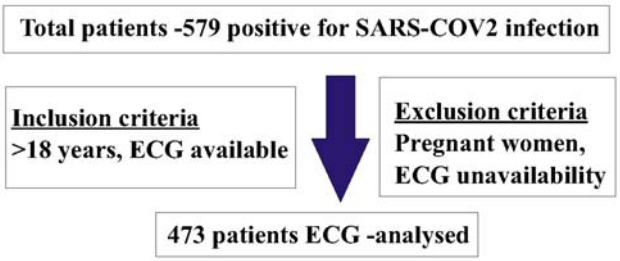

Fig 1 — Flow pathway of ECG in COVID-19 patients

288 patients (60.9%**)** were male and 185 (39.1%) were female. The mean age of the patient was 45 ± 16 years. Out of 473 patients, 59% (279) had no comorbidities and 41.9% (194) had comorbidities like Hypertension (HTN) and Diabetes Mellitus (DM) (18%), Chronic Obstructive Pulmonary Disease (6.6 %), Chronic Kidney Disease (5.1%), old Cerebrovascular Accident (2.8%), Coronary Artery Disease (2.3%), Hypothyroidism (1.3%). Depending on the COVID-19 severity they were classified into four categories Cat-A 186 patients (39.3%), Cat-B 110 patients (23.3%), Cat-C 121 patients (25.6%), Cat-D 56 patients (11.8%) (Fig 2)(Table 1).

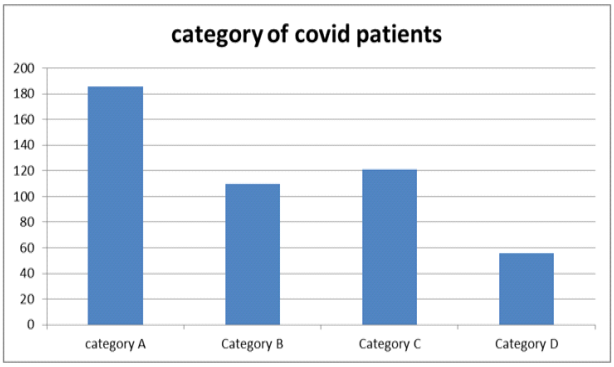

Fig 2 — Category of COVID-19 patients

Table 1 — *Baseline characteristics*		
Mean age	45+16 years	
Sex	Male 288 (60.9%)	Female 185 (39.1%)
Comorbidities	No 279 (59.1%)	Yes 193 (40.9%)
ECG changes	Normal 227 (48)	Abnormal 245 (52%)

Table 2 shows the various ECG findings in all categories of COVID-19 patients.

Among all patients, 365 survived (77.2%) while 108 patients (22.8%) succumbed to COVID-19 related complications. 32.6% of patients received mechanical (invasive and non-invasive) ventilation and 67.4% were not requiring any ventilatory assistance, just managed with oxygen support or without it. The ECG was normal in 48% and abnormal in 52% of the patients. Most common abnormal ECG finding was Sinus Tachycardia (19.5%) and less common findings were Sinus Bradycardia (5.3%), incomplete RBBB(3.2%), atrial fibrillation(2.5%), complete RBBB(2.3%), atrial premature complexes (2.3%), S1Q1T3 pattern (2.1%), first degree AV block (1.5%), ST-T wave changes (1.3%) with acute inferior wall MI was also reported (Fig 3).

In this retrospective single centre study of those patients with hospitalization, most common ECG finding with comorbidities was Sinus Tachycardia (19.5%) and without comorbidity was normal Sinus Rhythm (69.2%). Similar to other studies the patients with comorbidities had a higher incidence of Arrhythmias[3]. Except group Cat A all other groups showed Sinus Tachycardia (Cat-B 23.6% *versus* Cat-C 32.2% *versus* Cat-D 28.6%) and it was the most common ECG finding. There was a significant difference between ECG changes and COVID-19 severity (p<0.005). Most common ECG finding in both expired and alive group patients was Sinus Tachycardia (27.8% *versus* 17%)and significant differences were seen between these groups (p<0.005). Those patients who received mechanical ventilation and were critically ill, most frequent findings were sinus tachycardia(30.5%), Sinus Bradycardia(9.7%), Atrial Fibrillation (6.5%), S1Q3T3 pattern (5.8%), atrial complexes (4.5%), RBBB (4.5%) which is similar to other studies[15,16] and it was statistically significant (p<0.005).In our study, most of the patients were Asymptomatic (39.3%) and fewer patients were included in Cat-D (11.8%). Based on the median age (40 years), the older (>40 years)group had significant abnormal ECG findings compared to the younger group(<40 years) and it was statistically significant (p-value <0.005).

Table 2 — *ECG findings in all categories*						
ECG finding	Total	Cat A	Cat B	Cat C	Cat D	Frequency
Normal	227	151 (31.92)	59 (12.47)	15 (3.17)	2 (0.42)	48.0 %
Sinus Tachycardia	92	11(2.32)	26 (5.49)	39 (8.24)	16 (3.38)	19.5 %
Sinus Bradycardia	25	4 (0.85)	2 (0.42)	12 (2.53)	7 (1.47)	5.3 %
Complete RBBB	11	2 (0.42)	2 (0.42)	7 (1.47)	0 (0)	2.3 %
Incomplete RBBB	15	4 (0.85)	3 (0.63)	7 (1.47)	1 (0.21)	3.2 %
ST-T wave changes	6	3 (0.63)	1 (0.21)	1 (0.21)	1 (0.21)	1.3 %
Atrial fibrillation	12	1 (0.21)	0 (0)	6 (1.26)	5 (1.05)	2.5 %
Atrial flutter	5	0 (0)	0 (0)	1 (0.21)	4 (0.85)	1.1 %
APCs	11	2 (0.42)	2 (0.42)	5 (1.05)	2 (0.42)	2.3 %
QT prolongation	5	0 (0)	1 (0.21)	4 (0.85)	0 (0)	1.1 %
$S_1Q_3T_3$ pattern	10	0 (0)	1 (0.21)	6 (1.26)	3 (0.63)	2.1 %
AVNRT	4	2 (0.42)	0 (0)	0 (0)	2 (0.42)	0.8 %
1st degree AV block	7	1 (0.21)	2 (0.42)	3 (0.63)	1 (0.21)	1.5 %
LVH+LAD	3	0 (0)	0 (0)	3 (0.63)	0 (0)	0.6 %
LVH	13	1 (0.21)	4 (0.85)	5 (1.05)	3 (0.63)	2.7 %
IVCD	1	0 (0)	0 (0)	0 (0)	1 (0.21)	0.2 %
QS complex	8	2 (0.42)	2 (0.42)	1 (0.21)	3 (0.63)	1.7 %
Bifascicular block	2	0 (0)	0 (0)	1 (0.21)	1 (0.21)	0.4 %
RBBB strain	1	0 (0)	0 (0)	0 (0)	1 (0.21)	0.2 %
RBBB + P pulmonale	2	0 (0)	1 (0.21)	1 (0.21)	0 (0)	0.4 %
LBBB	1	0 (0)	0 (0)	1 (0.21)	0 (0)	0.2 %
P pulmonale	3	0 (0)	0 (0)	1 (0.21)	2 (0.42)	0.6 %
Low voltage	6	1 (0.21)	3 (0.63)	2 (0.42)	0 (0)	1.3 %
VPCs	1	0 (0)	1 (0.21)	0 (0)	0 (0)	0.2 %
RVH	1	1 (0.21)	0 (0)	0 (0)	0 (0)	0.2 %
Collapsed (Not available)	1	0 (0)	0 (0)	0 (0)	1 (0.21)	0.2 %
Total	473	186(39.3%)	110(23.3%)	121(25.6%)	56(11.8%)	100 %

Discussion

We present a detailed analysis of ECG findings of 473 COVID-19 patients, from the ECG done at the time of admission. Myocardial abnormalities, ECG changes, and arrhythmic responses in SARS-CoV2 infection might be due to hypoxic injury, Cytokine Storm (hyperinflammatory state), or direct myocardial injury while other contributory factors might be electrolyte abnormalities, myocardial depression, plaque rupture, coronary spasm, microthrombi or direct endothelial injury[10]. ECG finding was normal in 48% of all patients and it might be due to the patients in the study being younger and asymptomatic without any previous medical issues. As with other studies, ECG findings were not common in younger patients. In our study, the most common finding was presence of sinus tachycardia, and it was common across all categories including those on ventilators. Factors responsible for tachycardia might be elevated body temperature, hypoxia, hypovolemia, hypoperfusion, increased myocardial oxygen demand, or anxiety associated[11]. Barman, *et al* showed that Sinus Tachycardia

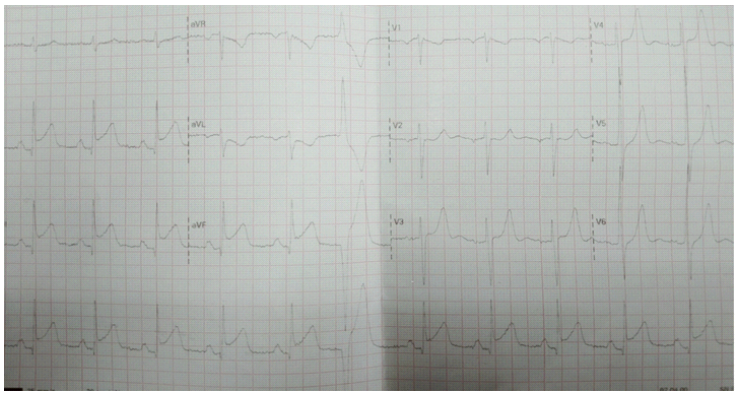

Fig 3 — ECG of a COVID 19 patient presented with acute STEMI-IWMI

was the most common finding[12]. Supraventricular tachycardias (AF, AFL, APCs, AVNRT) account for 6.7% of all patients. Yuan *et al* analyzed new ECG changes in 455 COVID-19 patients and found that 13% developed new-onset AF. Abrams, *et al* in their study has shown AF/AFL was seen in 14.3% of patients at the time of admission and was of new-onset in 10.1% during hospitali-zation[13]. In COVID-19 related illness and pulmonary embolism Sinus Tachycardia and/or atrial fibrillation with rapid ventricular response were commonly seen[14-17].

In our study Sinus Bradycardia was present in 5.3% of patients, however, no case of high-grade AV block was observed. A study showed that Bradyarrhythmias and atrioventricular block were less common when compared to Tachyarrythmias, but the incidence was reported up to 12%[18,19]. A recent case report in a COVID-19 patient showed first degree AV block progressing finally to third-degree AV block[18]. Similar to others, elderly patients with multiple risk factors had a higher risk of developing Bradyarrhythmias and AV block. These rhythm disturbances might be a marker of critically ill COVID-19 patients and in those having a high risk of Cardiovascular Collapse. In our patients, S1Q3T3 pattern, in isolation or associated with Right Bundle Branch Block (RBBB), or isolated RBBB (complete or incomplete) were considered signs of acute Right Ventricular Pressure Overload (RVPO), and 44 patients (9%) had signs of RVPO with p pulmonale (Fig 4).

RVPO related ECG changes may be due to prior reactive airway disease, hypoxia-induced vasoconstriction of pulmonary vessels, pulmonary vascular occlusion caused by the hypercoagulable state, higher PEEP related to ventilation. Similar to other studies, the ECG features of RVPO was more frequent in the patients receiving ventilation for severe COVID-19 Pneumonia which was statistically significant ($P<0.005$)[20]. Among all, 154 (32.6%) patients were put on ventilators and 26 patients (16.1%) had RVPO related ECG changes. The frequency of QTc prolongation in our patient population was less common (1.1%) as the mean age of the patients, comorbidities, and the incidence of drug toxicity were lower, and also as in other studies, the incidence of QTc prolongation is very low with the use of non-cardiovascular drugs (0.001%)[21]. In comparison to survivors (365), non-survivor (108) group had a lower incidence of ST-T-related ECG changes (4 patients *versus* 2 patients. It might be related to previous cardiac illness and this finding was contradictory to other studies, which showed that the ST depression detected in ECG is a marker of cardiac injury and can be used as an indicator of prognosis in these patients[12]. The incidence of low voltage complexes was also not specific (1.3%) and might be due to coexisting hypothyroidism, pre-existing obstructive airway disease or maybe due to invasive ventilation. The other ECG changes were seen like LVH, RVH, LBBB, QS complexes, VPCs, and IVCDs were incidental and might be pre-existing. As in other studies, in our study also the incidence of abnormal ECG findings was more common in the elderly group, with comorbidities, those who stayed more in the hospital, related to the severity of COVID-19 infection, received mechanical ventilation and in non-survivors. Limitations of this study is that its a single-center cross-sectional retrospective study comprising the population of less critically ill patients. Most of the patients in this study were asymptomatic, younger, without comorbidities and those with comorbidities at the time of hospitalization were not having their previous ECGs available for comparison and the ECG was taken at the time of admission lacking the follow-up data. However, available published literature has shown a low incidence of new ECG change in hospitalized COVID-19 patients. More rigorous studies of COVID-19 patients are imperative

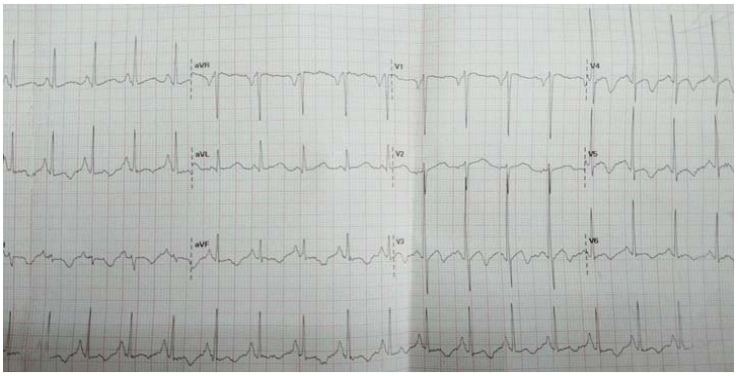

Fig 4 — ECG of a COVID-19 on mechanical ventilation shows Sinus tachycardia, acute RV pressure overload changes (P PULMONALE)

comparing pre-COVID ECGs (if available), with ECGs after getting infected with COVID and during follow-up to reveal the true impact of COVID related ECG changes on patient outcomes.

Conclusions

COVID-19 has affected millions of lives across the Globe. Many patients hospitalized with COVID-19 infection have developed cardiac abnormalities and related ECG changes. Identifying ECG patterns that might be related to COVID-19 is vital. This study tried to find out relevant ECG findings associated with COVID-19 and to correlate these Electrocardiographic abnormalities with their severity. Most common finding was sinus tachycardia but others included SVTs such as Atrial fibrillation or flutter, ventricular arrhythmias such as VT or VF, bradycardia, interval and axis changes (QT prolongation) and ST-segment and T wave changes. Knowledge of these findings may assist clinicians in the evaluation, management and prognostication of COVID-19 infected patients. Larger studies comparing pre, post and follow-up ECGs of COVID-19 infected patients are needed for better management and treatment outcomes.

Ethics Approval and Consent to Participate : The project was approved by the Institutional Scientific Advisory Committee as well as the Institutional Ethics Committee. The study protocol was approved by the Clinical Trial Screening and the Ethics Committee of the hospital.

Availability of data and material : The data underlying this article will be shared on reasonable request to the corresponding author.

Competing interests : none declared

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Original Article

Microbial Profile of Neonatal Septicemia and its Antibiogram Prevalent in a Tertiary Care Hospital of Western Odisha

Tanushree Ghosh[1], Swetalina Jena[2], Aruna Rani Behera[3], Sangeeta Panigrahy[4], Rajesh Kumar Sethi[5]

Introduction : A disseminated disease with positive Blood Culture during the first month of life and encompasses various systemic infections of the newborn such as septicemia, meningitis, pneumonia, arthritis, osteomyelitis and Urinary Tract Infection is defined as Neonatal Sepsis. It is one of the leading causes of morbidity and mortality amongst neonates of developing countries.

Aim : To determine the microbial profile of Blood Culture-positive Septicemia cases and study their antimicrobial susceptibility pattern.

Materials and Methods : Blood Culture and C-reactive Protein (CRP) estimation were done for all 220 clinically suspected neonates. All the pure Bacterial and Candida isolates were identified using standard biochemical tests. Antimicrobial susceptibility testing was done for all bacterial isolates using the Kirby-Bauer disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results : Out of 220 cases, 68.2% were culture positive. Early-onset Neonatal Septicemia (EONS) cases were 74% and Late-onset Neonatal Septicemia (LONS) 26%. The male to female ratio was 1.9:1. Bacterial cases were 66% and 34% were due to *Candida*. Gram-negative isolates predominated, with *Klebsiella pneumonia* being the most common one. In the case of Gram-positive isolates, *Staphylococcus aureus* was most common. The best overall sensitivity of Gram-negative isolates was to Amikacin (100%), Colistin (100%), and Imipenem (96%). Gram-positive isolates reported 100% sensitivity to Vancomycin, Teicoplanin and 97.4% to Linezolid.

Conclusion : Gram-negative isolates were the leading cause of Sepsis in our study. Strict antimicrobial stewardship should be implemented to prevent the emergence of multi-drug resistant strains.

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Key words **: Neonatal septicemia, Blood culture, CRP, Antimicrobial susceptibility.**

A disseminated disease with positive Blood Culture during the first month of life and encompasses various systemic infections of the new born such as Septicaemia, Meningitis, Pneumonia, Arthritis, Osteomyelitis and Urinary Tract Infection is defined as Neonatal Sepsis[1]. The first 28 days of life (neonatal period), represents the most vulnerable time for a child's survival. In 2013, roughly 45% of under-five deaths occurred during this period. The proportion of child deaths which occur in the neonatal period has increased in all WHO regions over the past 20 years[2]. According to National Neonatal Perinatal Database (2002-2003) the incidence of Neonatal Sepsis in India was 30 per 1000 live-births and total neonatal deaths in developing countries was 30-50%[3-5]. It is estimated that about 20% of neonates develop Sepsis and Sepsis related death are approximately 1%[6]. When onset of septicemia occurs within the first 72 hours of life, ie, Early Onset Septicemia (EOS) prenatal factors mainly predominate, when onset is after 72 hours of life, ie, Late Onset Septicemia (LOS) it mostly points towards postnatal infection or Nosocomial infection[7]. Maternal risk factors include fever, bacteriuria, Premature Rupture Of Membrane (PROM), amnionitis, prolonged labour, poor hygiene and genitourinary colonization

Editor's Comment :

- Neonatal Septicemia is one of the leading causes of neonatal mortality world wide, therefore our aim was to study in depth the various treatment and management options available. Strict antimicrobial stewardship should be implemented to prevent the emergence of multidrug resistant strains.

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with micro organisms[8]. Neonatal risk factors include prematurity, low birth weight, congenital anomalies, male sex and birth asphyxia[9].

Bacterial causative agents vary from institution to institution but commonly found organisms are Gram negative rods like *Escherichia coli, Klebsiella pneumoniae*, *Enterobacter species, Pseudomonas*, *Proteus*, *Citrobacter* and *Serratia* comprising of two thirds of cases of Septicemia and one third cases by Gram positive organisms like *Staphylococcus*, *Streptococcus*, *Listeria monocytogenes*[10]. Clinical presentation may be silent in a very small baby who may suddenly die without exhibiting any signs. In others, there is change in behaviour and feeding pattern like refusal to suck, unresponsiveness, lethargy, pallor and vacant stare[11]. Early Onset Sepsis (EOS) is more likely associated with respiratory distress. Hypothermia is a common manifestation in preterm babies while term babies may manifest with Fever, Diarrhoea, Vomiting, Abdominal distension, Jaundice and episodes of apneic spells with cyanosis. Only about half of the babies of proven sepsis are febrile, about 15 percent have hypothermia, remaining may be normothermic. Signs of meningitis is seen in less than one-third of babies[12]. The most important and dependable diagnostic parameter for Neonatal Septicemia is positive blood culture[13]. However, it is time consuming, requiring at least 48 to 72 hours to generate final report. For emergency management of the case, empirical antimicrobial therapy is generally started immediately after inoculating blood sample for culture, but the treatment needs to be modified after receiving the final blood culture and sensitivity report[14]. The outcome depends on the weight and maturity of the infant, type of etiologic agent, its sensitivity pattern and adequacy of supportive and specific therapy[15]. Specific complications include shock, adrenal insufficiency, consumptive coagulopathy, congestive heart failure, hyponatremia, etc[16]. Keeping in view the above facts the present study was designed with the following aim: To determine the microbial profile of septicemic neonates admitted to Neonatal Intensive Care Unit (NICU) of VIMSAR, Burla, and to undertake antimicrobial sensitivity testing of the microorganisms isolated.

Materials and Methods

This was a hospital-based cross-sectional study conducted over a period of 2 years, from November, 2013 to October 2015, at the Department of Microbiology, VIMSAR, Burla, after getting approval from the institutional Ethics Committee with no. IEC/IRB- 50/13.

Study group : The study group comprised 220 neonates admitted to VIMSAR, Neonatal Intensive Care Unit with clinical signs of Septicemia.

Inclusion criteria : All the neonates who were admitted with clinical signs of Sepsis.

Exclusion criteria : Neonates born to mothers who had received Antenatal Antibiotic Therapy within 48 hours prior to delivery and symptomatic neonates who had been started on antibiotics.

The diagnosis of Neonatal Septicemia was based on clinical criteria like poor activity, lethargy, inability or poor sucking, hypothermia, abdominal distension, and diminished or absent Neonatal Reflexes.

Media preparation : Brain Heart Infusion Biphasic Media (BHIBPM) culture bottles were used for performing Blood Culture. Commercially available Brain Heart Infusion (BHI) dehydrated media obtained from Himedia, (India) was used as per instruction[17].

Specimen collection and Transport : Any peripheral vein was chosen as the venepuncture site. The site was cleaned and disinfected with povidone-iodine followed by 70% Isopropyl alcohol and allowed to dry. Two milliliters of blood was collected with the help of a sterile disposable scalp vein (24G) and syringe (2 ml.) and immediately transferred to BHIBPM. Then the bottles were shaken gently to mix the blood with the broth homogeneously and transferred to the Microbiology laboratory in an upright position for incubation and culture[18].

Culture : In the laboratory the, bottles were incubated at 37°C for a maximum period of 7 days. The bottles were observed daily for signs of growth like turbidity, air bubbles and colonies on the surface of the sedimented red cells or over the solid slant portion of the biphasic medium. As soon as growth was observed, subculture was done on Blood agar and CLED agar plates and incubated at 37°C[19]. The bottles that showed no growth for 7 days were discarded.

Identification : Isolates were identified by their characteristic appearance on the respective media, Gram staining, and confirmed using standard biochemical tests[19]. For Gram-positive bacteria catalase, coagulase bile aesculin and other tests were performed. Gram-negative isolates were identified by motility test, indole production, citrate utilization, oxidase, sugar fermentation, and other tests. In the case of Candida isolates first of all Germ tube test was done to differentiate Candida albicans from Non-albicans. Carbohydrate Assimilation and Carbohydrate Fermentation test was done for further speciation[20].

Antibiotic Sensitivity Testing: The antimicrobial sensitivity testing was done for all pure bacterial

isolates in Mueller- Hinton agar plate by using Kirby-Bauer disk diffusion technique. The antibiotic discs used were obtained from Himedia (India) Laboratories. The sensitivity pattern was studied depending on the zone of inhibition as per the standard CLSI guidelines[21]. The antibiotic discs used in the study were:

Ampicillin (10µg), Amikacin (30µg), Amoxycillin/ Clavulanic acid (20/10µg), Ciprofloxacin (5µg), Cefuroxime (30µg), Cefotaxime (30µg), Cefoxitin (30µg), Colistin (10µg), Gentamicin (10µg), Imipenem(10µg), Linezolid (30µg), Piperacillin/ Tazobactam (100/10µg), Teicoplanin (30µg), Vancomycin (30µg).

CRP (C-reactive protein) estimation: TURBILYTE-CRP, a turbidimetric immunoassay for the determination of C-reactive protein based on the principle of latex agglutination was performed for each suspected neonatal septicemic case at the same time when blood was sent for culture.

Statistical Analysis: Data were collected in a Microsoft Excel sheet. Results expressed in percentage and ratio.

Results

During the study period, 220 newborns with clinical sepsis were admitted. Blood cultures were positive in 150 cases.(68.2%). Out of 150 cases, 111(74%) were having EOS and 39 (26%) were having LOS. Among the culture-positive cases, 98 (65.3%) were male and 52 (34.6%) were female neonates (Table 1). The ratio of male to female babies was 1.9:1.

Table 1 — *Age at onset of Septicemia in neonates of both sexes*

Age at onset of sepsis	Total number of cases (%)	Number of male babies	Number of female babies
0-3 days(EOS)	111 (74%)	70	41
4-28 days(LOS)	39 (26%)	28	11
Total	150	98	52

In 92 (61%) of the culture-positive cases were low birth weight and 58 (39%) were of normal body weight (Table 2).

Table 2 — *Distribution of culture-positive neonates in relation to birth weight*

Birth weight	Number of cases (%)
<2500gm (LBW)	92 (61%)
>2500gm (Normal)	58 (39%)
Total	150

Out of the 150 culture-positive cases, 81(54%) were preterm and 69 (46%) were term babies (Table 3).

The detailed etiology of the 150 culture-positive isolates was as follows: bacteria were 99 (66%) and

Table 3 — *Distribution of culture-positive neonates in relation to Gestational age*

Gestational age in weeks	Number of cases (%)
<37 weeks (Preterm)	81 (54%)
>37 weeks (Term)	69 (46%)
Total	150

51 (34%) were various species of candida. Among the bacterial isolates, 60 (60.6%) were Gram-negative bacilli and 39(39.4%) were Gram-positive cocci. In the case of Gram-negative bacilli, *Klebsiella pneumoniae* 34 (34.3%) and among Gram-positive cocci *Staphylococcus aureus* 26 (26.3%) were most commonly isolated. The rest of the pathogenic bacteria isolated in descending order were *Escherichia coli* 19 (19.1%), *Coagulase-negative Staphylococcus* 11(11.1), *Acinetobacter species* 3 (3.03%), *Citrobacter species* 3(3.03%), *Enterococcus species* 2(2.02%), and *Serratia species* 1(1.01) (Table 4).

Table 4 — *Pathogenic bacteria isolated from Blood culture*

Bacteria	Number (%)
Klebsiella pneumoniae	34 (34.3%)
Staphylococcus aureus	26 (26.3%)
Escherichia coli	19 (19.1%)
Coagulase negative staphylococcus	11 (11.1%)
Enterococcus species	2 (2.02%)
Serratia species	1 (1.01%)
Acinetobacter species	3 (3.03%)
Citrobacter species	3 (3.03%)
Total	99

Out of the 51(34%) pathogenic Candida species isolated, 18 (35.3%) were *Candida tropicalis*, followed by *Candida kruzei* 11(21.6%), *Candida parapsilosis* 9(17.6%), *Candida albicans* 7(13.7%), and *Candida glabrata* 6(11.8%) (Table 5).

Table 5 — *Pathogenic Candida species isolated from blood culture*

Candida species	Number (%)
Candida tropicalis	18 (35.3%)
Candida albicans	7 (13.7%)
Candida kruzei	11 (21.6%)
Candida parapsilosis	9 (17.6%)
Candida glabrata	6 (11.8%)
Total	51

Antibiotic susceptibility pattern was studied for all bacterial isolates causing Neonatal Septicemia.

For the Gram-negative isolates (Total no. 60), the highest sensitivity was reported for Amikacin (100%), Colistin (100%), Imipenem (96.7%), followed by Gentamicin (86.7%), Ciprofloxacin (86.7%), Amoxycillin/Clavulanic acid (48.3%). Out of the total Gram-negative isolates, 40% were ESBL producers. The highest resistance was observed to Ampicillin (100%)(Table 6).

Table 6 — *Antimicrobial sensitivity pattern of Gram negative bacilli (N=60)*

Antibiotic	Number of organisms sensitive (%)
Amikacin	60 (100%)
Gentamicin	52 (86.7%)
Cefotaxime	5 (8.3%)
Cefuroxime	4 (6.7%)
Ciprofloxacin	52 (86.7%)
Piperacillin/Tazobactam	51 (85%)
Amoxycillin/Clavulanic Acid	29 (48.3%)
Imipenem	58 (96.7%)
Ampicillin	0 (0%)
Colistin	60 (100%)

For Gram-positive isolates, the highest sensitivity was reported for Vancomycin (100%), Teicoplanin (100%), Linezolid (97.4%) followed by gentamicin (95%), and Amoxicillin/clavulanic acid (79.4%).

Methicillin-resistant Staphylococcus aureus was reported in 33.3% of the cases (Table 7).

Table 7 — *Antimicrobial sensitivity pattern of Gram positive isolates (N=39)*

Antibiotic	Number of organisms sensitive (%)
Gentamicin	37 (95%)
Ciprofloxacin	29 (74.4%)
Amoxycillin/Clavulanic Acid	26 (66.7%)
Cefoxitin	26 (66.7%)
Vancomycin	39 (100%)
Linezolid	38 (97.4%)
Teicoplanin	39 (100%)

CRP estimation was done for 220 clinically suspected neonates and it was correlated with Blood culture positivity (Table 8).

Table 8 — *Correlation of Blood culture with CRP*

	Blood Culture positive	Blood Culture negative
CRP positive	142	40
CRP negative	8	30

Sensitivity, Specificity, Positive Predictive value (PPV) and Negative predictive value (NPV) for CRP were 94.66%, 42.85%, 78.02%, and 78.94% respectively.

Out of the 150 culture-positive cases, death occurred in 17 (11.3%) neonates.

Discussion

Early diagnosis and therapy are essential for the prevention of morbidity and mortality due to neonatal sepsis in the Neonatal Intensive Care Unit (NICU).

Out of 220 clinically suspected cases of neonatal Sepsis in our study, 150 were Culture positive with a Blood Culture positivity rate of 68.2%. This finding correlates well with the study of other workers like Premlatha DE *et al*,- 72.3%[22]. EOS culture-positive cases were 74% and 26% were LOS. A higher prevalence of EOS was also reported by another study like Galhotra S *et al*,[23]. The ratio of culture-positive Male to Female babies was 1.9:1. Similarly, Buch *et al* found a Male to Female ratio of 1.8:1[24]. Several explanations had been laid down for higher male susceptibility, it may be due to a gene located on the X Chromosome involved in the synthesis of immunoglobulins in the male infants thus conferring less immunological protection compared to females[25].

In this study it was observed that low birth weight babies were more prone to Sepsis, observed frequency in the present study was 61%, comparable to the study done by Tallur SS *et al*, -55%[26]. The immature cellular immunity and low level of immunoglobulin (IgG), excessive handling and contaminated incubators expose them to infecting organisms, thus increasing infections rate. Second, to low birth weight, prematurity is the most important predisposing factor for Septicemia. In the study, preterm neonates accounted for 54% of the cases. This coincides with, a study by Khinchi YR *et al*,- 54.6%[27]. It has been established that several phagocytic functions are impaired including chemotaxis, phagocytosis and bacterial killing in preterm neonates. Also, there is impaired opsonic activity of the serum in pre-terms which is attributed to low levels of complement factors and partly to antibody deficiency. Stoll BJ[28].

In this study out of the 150 culture-positive cases, 66.4% were Bacteria and 33.6 % were Fungal isolates. Similar studies done in the past by workers like R Rani *et al* reported 62.3% Bacterial and 37.7% Fungal agents[29]. Changing trends of higher incidence of candidemia may be due to indiscriminate use of broad-spectrum antibiotics in neonatal septicemic cases.

In our study, Gram-negative isolates predominated (60.6%). *Klebsiella pneumonia* (34.3%) is most commonly isolated. This Gram-negative preponderance was also reported by Sriram R[30]. Amongst Gram-positive isolates, our study reported *Staphylococcus aureus* (26.3%) as the most common one. This is in accordance with the study done by Agnihotri N, *et al*, who reported 35% as *Staphylococcus aureus*[31]. Out of the total 51 (34%) Candida species reported in our study, the highest was *Candida tropicalis* (35.3%). This was similar to the findings of Jain A *et al*, who reported *Candida tropicalis* as the most common isolate[32].

Regarding the Antibiotic susceptibility pattern of the Gram-negative isolates in our study: 100% sensitivity was reported for Amikacin, Colistin followed by Imipenem (96%). These isolates reported 100% resistance to Ampicillin. This is in concordance with

the finding of other workers like Rasool KH, *et al*,[33]. 40% of the Gram-negative isolates were ESBL producers. This was mostly due to the indiscriminate use of third-generation cephalosporins. Our finding corroborated with the findings of Rao YK *et al*, who reported 45.8% ESBL[34].

Gram-positive isolates in our study were 100% sensitive to Vancomycin, Teicoplanin and 97.4% sensitive to Linezolid. These results are very much similar to the study done by Shaw CK[35]. Out of the 26 *Staphylococcus aureus* isolated, 33.3% were found to be Methicillin-resistant Staphylococcus aureus (MRSA). This finding is comparable to the findings of Kayenge N, *et al*, where 28% MRSA was reported[36].

In our study, we also did an estimation of C-reactive protein for all the clinically suspected cases and it was correlated with the Blood Culture reports.

Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) for CRP were 94.66%, 42.85%, 78.02%, and 78.94% respectively. These findings were in concordance with the findings of Mehrotra G[37]. Overall mortality rate in culture-positive cases was 11.3%. This coincides with the mortality rates of studies done by Bhat R, *et al*, and Khinchi YR[28,38].

Conclusion

Neonatal Septicemia being a major killer accounting for one-fourth to nearly half of the neonatal deaths in a developing country like ours, endeavors for rapid diagnosis and appropriate antimicrobial therapy is mandatory. Priority should be laid on the rapid diagnosis of suspected Sepsis cases using Blood Culture, especially when the neonates are of low birth weight, pre-term and male babies. Brain Heart Infusion Biphasic Media can be used for routine culture instead of using only Glucose broth or any other monophasic media, in order to have a rapid and higher rate of Culture positivity. In our study, Gram-negative bacilli were the predominant organism causing Septicemia with Extended-spectrum Beta-lactamase producing *Klebsiella pneumoniae* being the commonest one.

We also reported a significant number of Methicillin-resistant *Staphylococcus aureus*, along with a substantial number of Neonatal Septicemia cases due to various species of Candida.

Antimicrobial sensitivity for Gram-negative isolates was highest for Amikacin, Colistin, and Imipenem. Gram-positive isolates showed maximum sensitivity to Vancomycin, Teicoplanin, and Linezolid.

Empirical antimicrobial therapy should be started as early as possible and then modified after receiving final blood culture and sensitivity reports. However indiscriminate use of antibiotics is always cautioned so as to prevent the emergence of more multi-drug resistant cases. Adherence to infection control policies, including attention to strict hand hygiene practices, and antibiotic stewardship is required to minimize the number of infections in hospitalized neonates.

Limitations of the study : Although we had Fungal isolates also in our study group, we could not perform the antifungal susceptibility testing.

Conflicts of interest : The author declares no conflicts of interest.

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Original Article

A Retrospective Study to find out Factors Affecting Maternal Mortality in a Tertiary Care Hospital in Ahmedabad City, Gujarat

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Background : Data pertaining to preventable causes of maternal mortality are valuable in each set up to design interventional steps for the significant reduction of the maternal mortality ratio.

Objectives : (1) To study the trend on Maternal Mortality Rate (MMR); (2) To find out the factors for the Maternal Mortality.

Material and Methods : A retrospective cross-sectional study of maternal death was conducted in the Obstetrics Department of Tertiary Care Hospital of Ahmedabad city. The data of total 9 years from 1st April 2013 to 31st January 2021 were taken in the study. Epidemiological factors and causes affecting maternal mortality were assessed through pretested questionnaire that includes parity, duration between admission and mortality etc.

Results: Maternal Mortality Rate (MMR) was 180.2 per 1 lac live births during the study period. Young mothersaged 20 to 30 years (78.5%), and rural residence (76.6%), multiparous mothers (66.7%)were at risk for Maternal Mortality. Obstetric haemorrhage (25.8%) was the most common cause whereas COVID-19 pandemic later on were indirect causes contributing to Maternal Mortality. Conclusion: Great Care should be taken for high-risk pregnancy like young age, multiparous women and also of postpartum women. Postpartum haemorrhage was the commonest direct cause of Maternal Mortality. Strengthening of existing obstetric care facilities, facility for easy transport, appropriate referral linkages are keys to reduce Maternal Mortality to further extent.

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Key words **: Maternal mortality, Postpartum haemorrhage, COVID-19, Multiparous, High risk.**

Health of women remains an overwhelming challenge, particularly in the developing world like India. It is a crucial situation that requires urgent attention and scrutiny, eliminating preventable cause of mother's mortality is a prime objective of maternal death scrutiny, surveillance and response[1]. Maternal death is described as" the death of a female at the time of pregnancy, childbirth or within 42 days of termination of pregnancy, irrespective of the duration and site of pregnancy, from any cause related to or provoked by pregnancy or its any form of management, but not from any accidental or incidental causes"[2].

Maternal Mortality is a reflection of the standard of care that is provided for obstetric service and quality by healthcare system. Among total maternal deaths of world occurred during pregnancy and childbirth, India accounts for 20% of them. Globally about 800 women die every day of preventable causes related to pregnancy and childbirth. Maternal Mortality has been reduced from 130 to 113 per 100,000 live births from the year 2014-16 to 2016-18 as per Sample Registration System report by Registrar General of India[3] which is significantly behind the target of less than 100 maternal deaths per 1 lac live births by 2015 as mandated in Millennium Development Goals (MDGs)[4]. Estimated 44,000 women's death annually in India that were due to causes that are related to pregnancy and childbirth such as severe bleeding, infections, complications from delivery and pregnancy induced hypertension and its complication such as severe pre-eclampsia, eclampsia. Most of these causes were preventable in nature[5]. There is a much need of skilled manpower such as trained health professionals and health worker and also improved quality of care during and after delivery to avoid these preventable causes of maternal death.

Editor's Comment :

- Ending preventable cause of maternal deaths can only be achieved if all reproductive females have accessibility to a core subset of excellent maternal health interventions spanning across the continuum of quality care from periconceptual to postpartum period. Reductionof maternal mortality from preventable causes is a main indicator in the Sustainable Development Goals.

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As per World Health Organization (WHO) announcement, identification of barriers that is cause for limited access to higher quality treatment facility and addressed at all levels of the health system to improve the health of the mother and outcome of pregnancy. Maternal health improvement is one of the important targets for Sustainable Development Goal (SDG) and an important issue that require to be addressed urgently[6]. The foremost target of the SDG is the reduction of the Global Maternal Mortality ratio to lower than 70 per one lac live births by the year 2030[7].

Direct maternal death is the result of a complication of pregnancy, delivery or management of the two. Indirect maternal death is a pregnancy related death in a patient with a pre-existing or newly developed health problem unrelated to pregnancy or non-obstetrical deaths. With objective of assessment of the causes of Maternal Mortality and to recommend the various measures to reduce the mortality among mothers.

Material and Methods

A retrospective cross-sectional study of maternal death was conducted in the Obstetrics Department of Tertiary Care Hospital of Ahmedabad city. The data of total 9 years from 1st April 2013 to 31st January 2021 were taken in the study. Each case was analyzed with respect to age, parity, antenatal registration, residence, mode of delivery, duration between admission of patient to mortality etc. Direct, indirect, associated causes and socio-demographic factors contributing to mortality were assessed and systemically analyzed through Epi Info™Version 7.2. Statistical analysis like Percentage, Rate were calculated.

Maternal Mortality Ratio (MMR) was calculated by occurrence of total maternal deaths per among one lac live births.

Results

Table 1 shows that in the present study the maximum number of maternal deaths, 73 (78.5%) occurred in the age group of 20-30 years followed by 14 (15%) deaths above 30 years of age.Young age group were involved due to early marriage, poverty and nutritional deficiency. 72% of deaths were in unbooked patients and belonged to rural areas 76.3%. About 30% of the maternal deaths occurred within 6 hours of admission in the hospital, pointing to the critical condition in which they were brought, while 24.7% yield within 7 days (Fig 1).

Table 1 — *Socio-demographic characteristics*

Characteristics	No of patient	Percentage
Age :		
Up to 19 years	06	6.4
20 – 30 years	73	78.5
>30 years	14	15
Parity :		
Primipara	28	30
Multipara	62	66.7
Grand-multi	03	3.2
Registration :		
Unbooked	67	72
Booked	26	27.9
Residence :		
Rural	71	76.3
Urban	22	23.7
Delivery :		
Abortions	4	4.3
Undelivered	23	24.7
Home delivery	16	17.2
Delivery hospital	50	53.7
Admission to mortality interval :		
<1 hour	09	9.7
1 to 6 hours	28	30.1
6 to 12 hours	17	18.3
12 to 24 hours	11	11.8
24 hours to 7 days	23	24.7
>7 days	05	5.3

As shown in Table 2, out of total maternal deaths, 29.1% were in antenatal period, out of them most of were from far-off area resulting in delayed treatment and intervention and women were in poor general condition at the time of admission.

As shown in Table 3, Direct obstetric causes were responsible for 61(65.6%) deaths, ie, obstetric complications of pregnancy, labour and puerperium. Among them, Haemorrhage 24 (25.8%), hypertensive disorders 19 (20.4%) and Sepsis 18(19.3%) were leading direct causes of mortality.

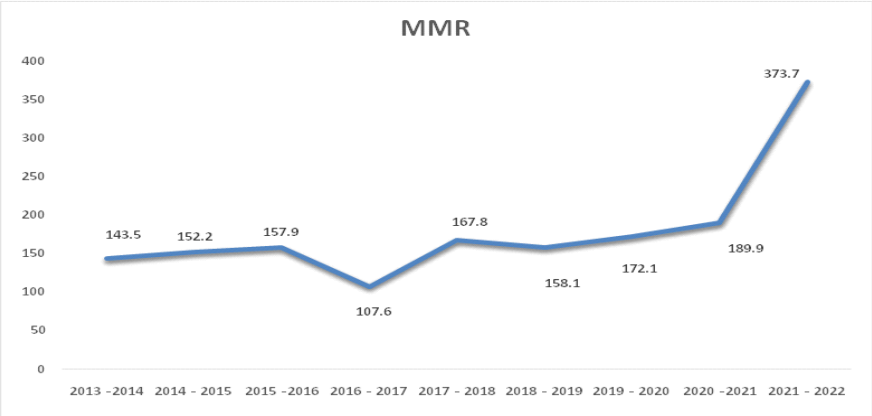

Fig 1 — Trend of Maternal Mortality Rate

Table 2 — *Period of death in pregnancy*

Year	Antenatal	Intrapartum	Postpartum
2013	2	0	5
2014	3	0	5
2015	3	1	4
2016	0	1	5
2017	0	0	10
2018	4	1	4
2019	5	0	7
2020	4	1	8
2021	6	4	10
2013-2021	27 (29.1%)	8 (8.6%)	58 (62.4%)

Around 34.4% of maternal death was due to indirect cause that is the result of pre-existing disease that developed during pregnancy, which are not due to direct obstetric cause but are aggravated by physiological effect of pregnancy. One of the most significant cause was anaemia (7.5%) (Fig 2).

Discussion

Of maternal deaths 73 (78.5%) occurred in 20-30 years age group such results were found in the study conducted by Parmar M *et al*[8]. Females having young age were at higher risk due to early age of marriage, poor families and malnutrition. 72% of deaths were in unbooked patients and belonged to rural areas 76.3%, increased number of maternal death in unregistered patients were noted in the study by Bhaskar K *et al*[9]. About 30% of the maternal deaths occurred within 6 hours of admission in the hospital, pointing to the critical condition in which they were brought, while 24.7% yield within 7 days.

Amongst total Maternal Mortality, 29.1% occurred in antenatal period, out of them most of were from area that were too far resulting in delayed management of case due to late arrival at health facility and pregnant females were in critical condition at the time of presentation. Sitaula S *et al* also noted that delayed referral and poor obstetric care was the main reason for postpartum deaths[10].

Table 3 — *Direct and Indirect causes of Maternal Mortality*

Direct cause 61(65.6%)	No of patients	Percentage
Haemorrhage	24	25.8%
Hypertensive disorder	19	20.4%
Sepsis	18	19.3%
Indirect cause 32(34.4%) :		
Anemia	7	7.5%
COVID-19 infection	7	7.5%
Heart disease	5	5.4%
Swine flu	4	4.3%
ARDS	3	3.2%
Hepatitis	2	2.2%
ARF	2	2.2%
Amniotic fluid embolism	1	1.1%
Pulmonary embolism	1	1.1%

Direct obstetric factors(complication developed during pregnancy, labour or puerperium)were responsible for 65.6% deaths. Among them, Haemorrhage (25.8%), Hypertensive disorders (20.4%) and Sepsis (19.3%) were major direct causes of maternal deaths. Other similar studies have shown variation in direct obstetrical deaths, 66.7% in a study by Verma K *et al*,[11] and 68.70% by Kulkarni *et al*[12].

Around 34.4% of maternal deaths were due to indirect causes resulting from pre-existing disease that developed during entire Antenatal period of Pregnancy, which are not due to direct obstetric cause but are provoked by Physiological effect of pregnancy. One of the most important causes was low haemoglobin level (anaemia) (7.5%). Other studies conducted by Ashok V, *et al* shows same anemia related death rate[13]. Heart failure and sudden death may occur due to pre-existing anemia in pregnant women. It also reduces the maternal ability to resist most of the infectious organism and cope up with severe blood loss[18]. Hepatitis accounted for 3.4% deaths which were tested HEV positive and eventually complicated with Hepatorenal Syndrome. 4.16% deaths have been reported in study of Bedi N *et al*[14].

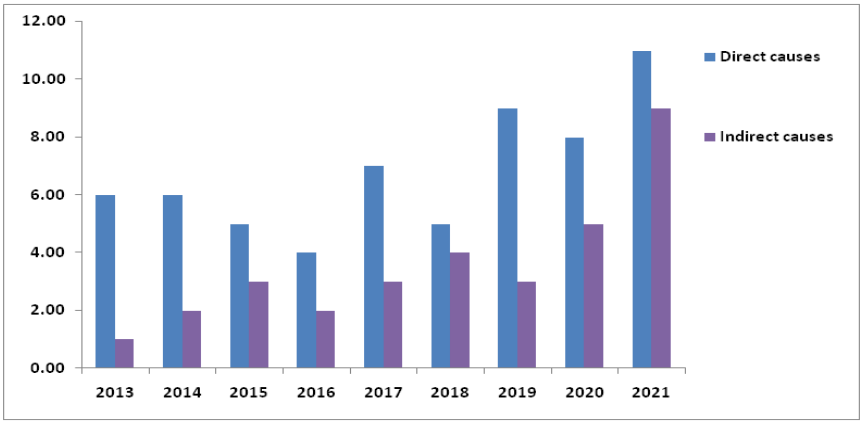

Fig 2 — Year-wise distribution of causes of death (Direct or Indirect)

The MMR of the studied hospital was 180.2 per 1 lac live births, which was significantly higher compared to national statistics as such institutions being a higher treatment care center where most of women (antenatal or intra natal) were referred from rural hard to reach areas leads to delayed rate of hospitalization and subsequent management. Many other comparative studies showing the varying MMR such as Shobha G *et al*-234.6,[15] Barsode S *et al*-

185.16[16]. Majority were multiparous (66.7%) as compared to primiparous women (30%). Similarly Nair A, *et al* reported 52.2% and 42.6% women multipara and primipara respectively[17]. Significantly higher number of pregnancies and short interval between successive pregnancies together adversely affect the maternal health and responsible for high fatality among mothers. Out of delivered patients, 12.9% were delivered in other hospital (PHC, UHC) and 12.2% home delivery found. Most of these were delivered without the services of a trained midwifery personnel. Deaths from incomplete and septic abortions were noted (4.3%) which might be due to lack of education, social stigma and delayed hospitalization. Such type of deaths can be minimized with proper awareness regarding contraceptive uses, family planning and medical termination of pregnancy (Table 1). Antenatal deaths can be prevented with early detection of warning signs of high-risk pregnancy such as Preeclampsia, Eclamspia, Placenta previa, Abruptio placenta, Intrauterine Death of Fetus (IUFD) etc,which requires early referral, easy transport and timely intervention at Tertiary Care Hospital where easy availability of blood bank and high-quality obstetric care by trained health personnel is made possible. Postpartum deaths reported for about 60% of total and12 of them were delivered at other hospital and referred to this institution with complication in postpartum period.

Other similar study done by Khandale SN et al found that three types of delay in referral of the patients to other higher centers leading to very high mortality among mothers[18]. Unfortunately, in most of the cases, type-1 delay of decision making to get help was the culprit.

Many direct obstetric causes were responsible (65.6%) for maternal death. Postpartum Haemorrhage is sudden, unpredictable and more serious in multiparity women. PPH also needs distinct focus because it may lead to mortality speedily if no provision for prompt life-saving procedure and care. It has the shortest reported episode to death interval (Table 1). Detection of antepartum haemorrhage and its advance management, referral to higher care center, active management of third stage of labour, detection of postpartum haemorrhage with appropriate surgical intervention and supportive treatment in HDU prevents many haemorrhage related maternal deaths. Gestational Hypertension particularly pre-eclampsia with severe features and its complication like HELLP syndrome causes more maternal morbidity and mortality (20.4%). Such mortality in our present study primarily found due to fail to detect associated symptoms/complications and late referral to higher treatment centre. Detection of Pre-eclampsia should be during scheduled antenatal visits and management should be appropriately done before onset of convulsions and other life-threatening sequelae. Out of total 18 Maternal Mortality due to sepsis, 5 were due to puerperal sepsis and 3 were from unsafe abortions which may result of poor hygiene and untreated Reproductive Tract Infections (RTIs). Uses of higher antibiotics and maintaining aseptic precautions during labour and postpartum period with counseling about proper hygiene to the patients can prevent Septicemia related deaths. To avoid abortion related maternal deaths all woman including adolescents needs access to contraception, safe abortion services delivered by qualified medical personnel and quality post abortal care.

Since December 2019, the whole world has faced a universal crisis after the finding a novel coronavirus, SARS CoV-2 that causes COVID-19, a disease with predominantly involving respiratory system. Current study finding showed that so far there have been 7.5% maternal deaths due to COVID-19 in 2020-2021, out of which 4 patients were admitted due to lack of O_2 saturation. Decision regarding termination of pregnancy in terms of emergency Cesarean Section was carried out for better outcome of mothers. However, the case was documented with death for which anaesthesia related complication could also be the reason. To put this in context, 4.3% H1N1 related maternal death in a 12 months period (Swine flu endemic in India, 2015). Here, it is reasonable to anticipate that the situation in 2020-21(373.7), were suddenly increasing MMR Contribute significantly of COVID-19 effect on pregnancy, childbirth and postpartum period (Fig 2). Pandemic context and the prioritization of COVID-19 on resource allocation within the Healthcare System may also impair antenatal quality of care by creating barriers to access routine antenatal appointments and laboratory tests. After WHO pandemic mandate, expert recommendations and guidelines from associations were released focusing management during pregnancy and postpartum period of mother[19].

Conclusion

Various factors responsible for maternal morbidity and mortality are preventable. Regular antenatal care, early detection of high-risk factors, timely intervention and referral to a Tertiary Care Hospital is needed. Aseptic precautions during operative procedures, use of antibiotics and proper operative techniques are to be used to minimize sepsis. All Antenatal women must

be educated regarding availability of Medical Termination of Pregnancy (MTP) services, which prevents incomplete and septic abortions. Death related to Hypertensive disorders of pregnancy and Obstetric haemorrhage can be prevented with early detection and availability of 24 hours blood bank facility at First Referral Unit (FRU). Apart from medical intervention, social, cultural, education, financial factors play crucial role in decreasing maternal death. Education regarding late marriage, contraceptive use, spacing pregnancy and limiting family size are important to save many lives. Equally important is to upgradation of the status of females in the society with emphasis on literacy and general health awareness.

National Health Mission (NHM) plays a significant role in achieving the lower Maternal Mortality by improving facilities of health care, hospital deliveries and timely refer high-risk pregnant women. The network of well-trained ASHA workers should be strengthened which form a link between pregnant women and health system. There is a need to address the nutrition of girls during their adolescence period for improvement as these are the girls who will be a mother of tomorrow.

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Conflicts of interest : NIL

Approval of Institutional Ethical Committee: Approved

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Original Article

Why MBBS Students are Taking to Substance Abuse ? — A Retrospective Study on the Pattern and Causes of Substance Abuse among the MBBS Students of West Bengal

Aditi Chaudhuri[1], Siddalingaiah HS[2], Ranjita Santra[3], Debasis Bhattacharyya[4]

Background : Substance abuse is an important health hazard and also a major preventable cause of morbidity and mortality. This habit not only affects health, education and occupational career, but also incurs huge financial and social burden to the society specially when the doctors are involved in it.

Aims and objectives : To estimate the prevalence of substance abuse, its pattern and causes among the MBBS students of West Bengal.

Methods : A questionnaire based cross-sectional retrospective study was designed to collect data from the Medical Officers of the State to record their experience of substance abuse during their MBBS course.

Results : The prevalence of substance abuse was 22% among the study participants. Smoking Tobacco was most common (16.67%). 76% of the subjects with substance abuse spend Rs1000 or less per month. The prevalence was 25% in upper class and 22.22% among those who belonged to lower class of socio-economic status as per BG Prasad Classification. Curiosity was the reason as per 34.5% of the subjects followed by depression (23.25%), peer pressure (13%) study pressure by 15%; media influence by 11%; to cope with home problems by 10.75% and parental influence by 2.25% of the study subjects.

Conclusion : The institution should keep a Psychological Counselor who can guide the students who suffer from problems related to Depression, Peer pressure, Study pressure that may lead to substance abuse. Allotting, hobbies, sports and recreation would help in keeping away from substance abuse.

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Key words **: Substance abuse, Tobacco smoking, Medical students, Alcohol abuse, Mental health.**

Psychoactive substance abuse is an important health hazard and a major preventable cause of morbidity and mortality. Despite the fact that the hazards of substance abuse are well known, the number of young people abusing psychoactive substances seems to be on the increase[1-6]. It is very important to study the pattern and proportion of substance abuse among the youth as the consequences of substance abuse are multifaceted. This habit not only affects health, education and occupational career, but also incurs huge financial and social burden to the society[2].

As the saying goes-today's young people are tomorrow's future, the growth of a nation depends on the health of youth. Professionals, particularly medicos with habit of substance abuse might be dangerous for others, as they might lose a sound judgment, fail in responsibility and cause harm to the service receivers. Situation could be disastrous when the addicted doctors become the decision makers of human lives and well beings[7].

A recent WHO estimate shows a burden of Worldwide psychoactive substance abuse of around 2 billion alcohol users, 1.3 billion smokers and 185 million drug abusers[6]. Studies conducted worldwide including India have estimated a prevalence rate of substance abuse to be around 20-40% among students from various streams including the medical field, however, these restrict themselves to tobacco or alcohol use and many of these are gender biased[3,4,6,8,9]. Previous studies have already found the reasons for drug usage which include peer pressure,

Editor's Comment :

- Substance abuse affects health, education, career of an individual and incurs huge financial and social burden to the society specially when the doctors are involved in it. The causes behind substance abuse are curiosity, depression and peer pressure which can be addressed by counselling and motivating students for more physical activities.

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depression, curiosity, media influence, parental influence, coping with home problems or study/ academic pressure[6,8,10-17].

With the above background, the present study was undertaken with the following objectives:

(1) To estimate the prevalence of substance abuse and its pattern among the students of all Medical Colleges of West Bengal.

(2) To determine the causes of substance abuse among the study population.

Materials and Methods

The study was conducted at Apex Training Institute of West Bengal which is the centre for induction training of freshly recruited Medical Officers in West Bengal. An observational, descriptive, cross-sectional study was conducted on the Medical Officers between October 2020 to September 2021. Since substance abuse is a sensitive issue, the sample size for conducting the present study was not determined before the study considering the uncertainty about the number of who will consent to the study. We decided on complete enumeration and included all 264 Medical Officers of the West Bengal Health Service who attended training during the study period and gave consent to participate in the study. Informed written consent was taken from the participants and they were administered a pre-designed, structured, validated and pre-tested questionnaire. Validation was done by 3 experts in this field. Study variables included socio-economic background, Age, Sex, Religion, Type of family, Number of family members, Residence, Per capita monthly income, Educational status – Mother, Father, Occupation – Mother, Father, Family history of substance abuse and behavioural characteristics such as addiction – Tobacco, Alcohol or any other. The participants were asked to recall about their experience of substance abuse if any during their MBBS period. Since all participants were freshly recruited in service after passing MBBS, their period of recall was not more than 7 years.

The study on substance abuse and its patterns among the study population was conducted with the following working definitions:

Substance Abuse : *Substance Abuse is defined as self-administration of a substance for eg. Tobacco smoking, Alcohol, Cannabis or any drug for non-medical reasons in quantities and frequencies which may impair an individual's ability to function effectively and which may result in social, physical, or emotional harm*[18].

Tobacco Smoking : *Inhalation of the smoke of burning Tobacco encased in Cigarettes, Bidis, Pipes etc. which cause physical addiction to Tobacco products.*

Smokeless Tobacco : *Tobacco products such as Chewing tobacco, Snuff, Creamy snuff, Tobacco gum and Gutka which deliver nicotine without smoke.*

Alcohol: Heavy drinking is defined, for instance, as drinking more than 40 grams of pure Alcohol per day for men and 20 grams of pure Alcohol per day for women[19].

Data Entry & Analysis : Data was entered in MS EXCEL sheet and analysis was done.

Ethics : The study was approved by the Institutional Ethics Committee prior to data collection.

Results

Table 1 shows the distribution of socio-demographic characteristics among the study population. It shows that 70% were male, 30% female. All subjects were in the age range of 18 to 23 years when they started substance abuse. Almost 75% belonged to Hindu religion and about 70% were Urban residents. Nearly 63% were hostellers and about 80% hailed from nuclear families with about 83% from families having 6 or less members. About 75% had Fathers with graduation or above education and about 54% with a Mother qualified with graduation or above. Most study subjects reported their Father to be a professional or in service or a businessman and majority reported their Mother to be a home maker. Nearly 77% of the study subjects belonged to upper or upper-middle class as per BG Prasad Scale for assessing socio-economic status. 21.97% reported a history of substance abuse in their families.

Fig 1 shows that the prevalence of substance abuse in the study population was 22%, with 59 subjects having substance abuse for one or more substances.

Fig 2 shows the prevalence of abuse of various different individual substances among the study population. Here, it can be seen that smoking Tobacco was prevalent among 16.67% subjects, which was the most abused substance and Alcohol abuse was prevalent among 12.5% of the study population. However, Cannabis and Smokeless tobacco were also being abused with a prevalence of 3% and 1.14% respectively among the study population.

Fig 3 shows the average range amount of money (in Rupees) spent by study subjects on substance abuse every month. It is evident that nearly three fourth (76%) of the subjects with substance abuse spend Rs 1000 or less per month and about one fourth (24%) spend more than Rs 1000 on their substance abuse behaviours.

Table 2 shows the prevalence of substance abuse

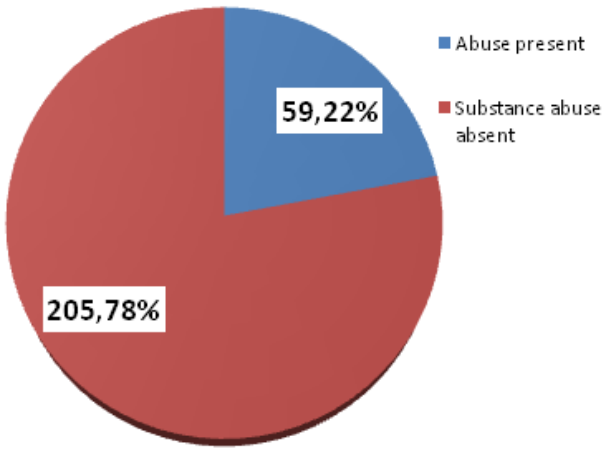

Fig 1 — Prevalence of substance abuse among study subjects (N=264)

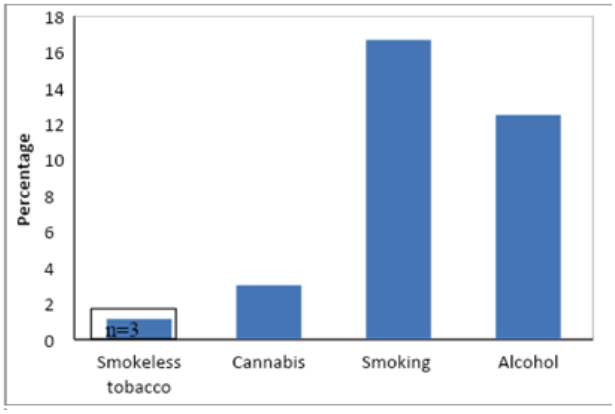

Fig 2 — Different substance wise prevalence of abuse among study participants (N=264)

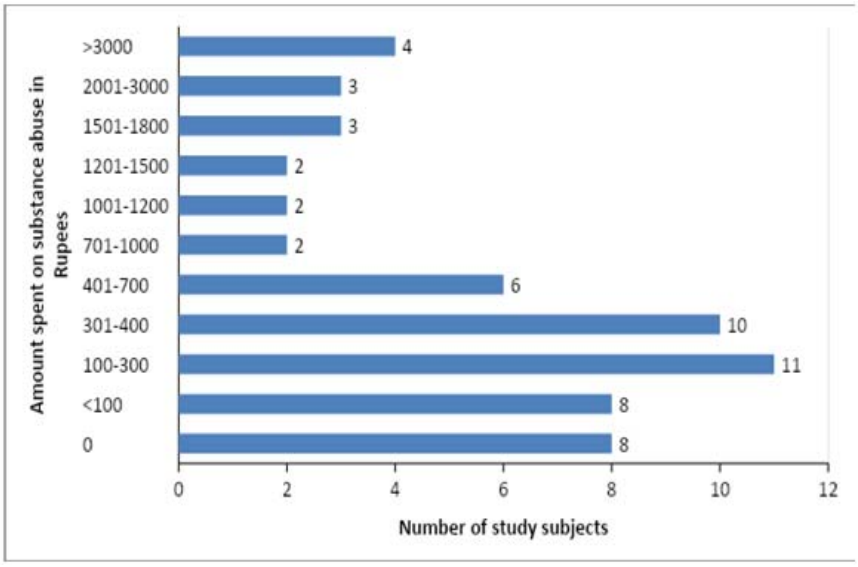

Fig 3 — Monthly expenditure (Rs.) on substance abuse by study participants (N=59)

among various categories of socio-demographic variables. It is evident that in males substance abuse was 27.56% when compared to females, which was 10.12%. This study included subjects in the age range of 19 to 23 years and the prevalence was highest in the age of 21, which was 32.35%. The prevalence was slightly higher in Hindu subjects at 23.5% than Muslim subjects, which was 18.65%. Prevalence of 60% among Christian subjects is probably due to very low representation in our study and hence cannot be commented.

It is evident from the Table 2 that the prevalence in subjects from Urban backgrounds was 22.95%. It is also evident that the prevalence was 28.20% in subjects who had joined in the year 2015. Prevalence was 23.35% among hostellers and 23% in those hailed from joint families. The prevalence of substance abuse when Father's and Mother's educational level is graduation or postgraduation is 22% and 22.76% respectively[20].

The prevalence of substance abuse was 30.8% among subjects with businessman Father and it was 23.81% when Mother was a professional. The prevalence was 21.97% in groups with family history of substance abuse. The prevalence was 25% in upper class and 22.22% among those who belonged to lower class of socio-economic status as per BG Prasad classification.

Table 3 shows that prevalence of Alcohol abuse was 12.5% among the study population. Initiation of Alcohol was in 19-21 age group for 54.55% of the study subjects. Nearly 72% consumed more than 100ml of Alcohol per day.

Table 4 shows that prevalence of Smoking was 16.67% among the study population. Initiation of Smoking was maximum (34.09%) in 17-19 age group for the study subjects. Nearly 52% smoked more than 3 cigarettes per day.

Fig 4 shows the reasons quoted by our study participants for the abuse of various substances of addiction. Curiosity was the reason as per 34.5% of the subjects; Depression was the reason quoted by 23.25%; peer pressure by 13%; study pressure by 15%; Media influence by 11%; to cope with Home problems by 10.75% and Parental influence by 2.25% of the study subjects.

Table 1 — *Socio-demographic characteristics of the study population (N=264)*

Parameter	Category	N	%
Sex	Male	185	70.07
	Female	79	29.93
Age (in years) when substance abuse started	18	16	6.06
	19	48	18.18
	20	83	31.44
	21	68	25.76
	22	31	11.74
	23	18	6.82
Religion	Hinduism	200	75.75
	Islam	59	22.35
	Christianity	2	0.75
	Others (Jain,Sikh,Buddhist)	3	1.15
Place of residence	Urban	183	69.32
	Rural	81	30.68
Year of admission in MBBS course	2010	76	28.79
	2011	117	44.32
	2012	71	26.89
Living arrangement	Hosteller	167	63.26
	Day scholar	97	36.74
Type of family	Nuclear	213	80.68
	Joint	51	19.32
Number of family members	≤3	70	26.52
	4-6	151	57.20
	7-9	27	10.23
	10-12	4	1.51
	13-15	5	1.89
	16-18	2	0.76
	19-21	4	1.51
	22 & above	1	0.38
Father's Education	Illiterate	5	1.89
	Pre-primary	0	0
	Primary	9	3.41
	Middle school	12	4.55
	High school	13	4.92
	Higher secondary	25	9.47
	Graduate or postgraduate	200	75.76
Mother's Education	Illiterate	7	2.65
	Pre-primary	2	0.76
	Primary	10	3.79
	Middle school	24	9.09
	High school	27	10.23
	Higher secondary	49	18.56
	Graduate or postgraduate	145	54.92
Father's occupation	Business	54	20.45
	Service	101	38.26
	Professional	75	28.41
	Skilled	32	12.12
	Unskilled	2	0.76
Mother's occupation	Business	1	0.38
	Service	34	12.88
	Professional	21	7.95
	Home-maker	208	78.79
Per capita monthly income (in Rupees)/ Socio-economical condition [B G Prasad scale]	<811 (Class V)	9	3.42
	812-1569 (Class IV)	21	7.95
	1570-2651 (Class III)	28	10.6
	2652-5356 (Class II)	39	14.77
	>5357 (Class I)	167	63.26
History of Substance Abuse in family	Yes	58	21.97
	No	206	78.03

Table 2 — *Distribution pattern of substance abuse among various categories of socio-demographic variables of study population (n=59)*

Variable	Category	Substance abuse present (n)	Prevalence (%)
Sex	Male	51	27.56
	Female	8	10.12
Age	18	1	6.25
	19	11	22.91
	20	13	15.66
	21	22	32.35
	22	7	22.58
	23	5	27.78
Religion	Hinduism	47	23.5
	Islam	11	18.64
	Christianity	1	50
	Others	0	0
Residence background	Urban	42	22.95
	Rural	16	19.75
Year of joining MBBS	2016	7	9.21
	2015	33	28.20
	2014	19	26.76
Stay arrangement	Hosteller	39	23.35
	Day scholar	20	20.61
Family type	Joint family	49	23
	Nuclear family	10	19.25
Educational level of father	Graduate and postgraduate	43	22
	Higher Secondary	8	32
	High School	2	15.38
	Middle School	3	25
	Primary	1	11.11
	Illiterate	3	60
Educational level of mother	Graduate and Postgraduate	33	22.76
	Higher Secondary	11	22.45
	High School	8	29.63
	Middle School	6	25
	Primary	0	0
	Illiterate	1	14.28
Father's occupation	Business	17	30.8
	Service	20	19.8
	Professional	16	21.3
	Skilled	5	16.7
	Unskilled	1	50
Mother's occupation	Home-maker	49	23.55
	Service	5	14.71
	Professional	5	23.81
Family history of substance abuse	Present	13	21.97
	Absent	46	22.33
Socio-economical condition [B G Prasad scale]	I(upper class)	42	25
	II(upper middle class)	5	12.82
	III(middle class)	5	17.65
	IV(lower middle class)	5	23.81
	V(lower class)	2	22.22

Discussion

We conducted a cross sectional study where the participants were asked to recall about their experience of substance abuse if any during their MBBS period. In the light of above results it can be said that one

Table 3 — *Prevalence and pattern of alcohol abuse ever among the study subjects (n=33)*

Parameter	Category	N	%
Alcohol abuse prevalence	Alcoholic	33	12.5
	Non alcoholic	231	87.5
Age of initiation of alcohol	<15	1	3.03
	15-17	6	18.18
	17-19	5	15.15
	19-21	18	54.55
	>21	3	9.09
Amount of alcohol consumed per day(ml/day)	<75	7	21.88
	75-100	2	6.25
	100-200	8	25
	200-500	10	31.25
	>500	5	15.62

Table 4 — *Pattern of smoking tobacco among the study subjects (n=44)*

Parameter	Category	N	%
Smoking history	Smokers	44	16.67
	Non-smokers	220	83.33
Age of initiation of smoking (years)	<15	3	6.8
	15-17	8	18.18
	17-19	15	34.09
	19-21	12	27.27
	>21	6	13.63
Number of cigarettes consumed per day	1-3	21	47.72
	4-7	10	22.7
	8-11	6	13.63
	12-15	3	6.8
	16-19	1	2.27
	≥ 20	3	6.8

fourth of the participants in our study were involved in substance abuse. Further, it can be said that male and hostellers were more prone to involve in substance abuse. Smoking and Alcohol were found to be the commonest form of substance abuse. Major causes for substance abuse were found to be curiosity to explore new things and depression due to several causes.

Our study population had an overall prevalence of 22% of abusing at least one or more of the harmful substances with higher rates among hostellers. In other studies[3] on Indian population, substance use was reported between 32.5% to as high as 81.2% among medical students, interns and house physicians. Mir *et al*[19] found in his study that the prevalence of substance abuse among the students were 25.9% and 76.6% of hostellers used harmful substances. The higher rate among hostellers may be due to lack of parental monitoring while staying away from home. The present study showed that the average monthly expenditure made on substance abuse by about three fourth of addicted individuals was up to about Rs.1000. In a study by Mohanty *et al*[8] 36.8% of abusers spent $7.39 to 14.79 a month on substance abuse.This points

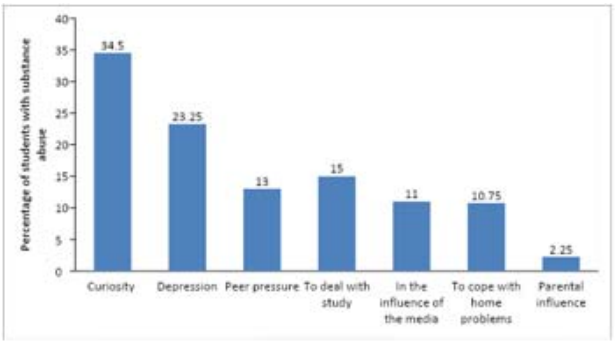

Fig 4 — Reasons for substance abuse among subjects with substance abuse (n=59, multiple answer type)

to easy availability of money with the students. Our study showed that Tobacco smoking was the most common method of substance abuse with 16.67% of the study population involved. Interestingly, 34.09% of the subjects started to abuse Tobacco smoking at the age of around 17 to 19 years. This probably indicates the increasing peer influences and course related stress among the study subjects as they moved beyond their 1st year of study. Similarly, according to Kumar[4] the most prevalent habit was consumption of smokeless tobacco substances. However, Mir *et al*[8] found that Alcohol was the single most preferred substance of abuse used by 36.40% of students. The present study revealed that curiosity was the most important reason for about one third of the subjects followed by Depression and Peer pressure. Similarly a study in Karnataka[21] showed that curiosity for experience (42.4%) was major reason for initiation of substance abuse. According to Basu and Kumar[3] stress due to situational, personal and professional issues, abuse and family history of Alcoholism were the major risk factors for substance abuse. Studying and understanding these factors are important as it might have a role in planning health promotion strategies for young adults especially in the initial years of professional courses, where the risk of onset of substance abuse is maximum.

Limitations of our study includes the possibility of recall bias and social desirability bias. The study includes doctors as participants and hence the results might have to be generalised with caution to other groups of adolescents and adults including general population. However, since substance abuse is a sensitive issue, the participants were more likely to give unbiased data at matured stage (medical officers) than when they were students. Also since we have a mixed pool of study population covering the students from various Medical Colleges of the state, the results can be generalised to the medical fraternity of the

state. Herein lies the novelty of the study.

Conclusion

As Depression and Peer Pressure is the very cause of substance abuse, this can be dealt with indulging more time in physical activities, hobbies, sports and recreation. The institutions should keep a Psychological Counselor so that if Students suffered from Peer-pressure, Depression or other issues they may share it with the Counselor and overcome the situation with proper guidance. Programs for raising awareness about ill effects of substance abuse needs to be organised for students and their parents as well. Students who are dependent on addiction both physically and psychologically should be recommended to visit rehabilitation center of psychiatric OPD. The victims can be counseled with Information, Education and Communication (IEC) and Behavior Change Communication (BCC) to bring the needed change in their behaviour.

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Original Article

All Gene Expression of Leukotriene A4 Hydroxylase (*LTA4H*) Gene in Extra Pulmonary Tuberculosis Patients and Healthy Control in North Indian Population

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Initial diagnosis and timely treatment of Extra Pulmonary Tuberculosis (EPTB) continues to be a challenge in all over World as well as India. First time, this analysis will discover the role of *LTA4H* gene and may be establishing another candidate that impacts the sensitivity to EPTB in the population of North India. This study will be the first report on *LTA4H* gene various diagnostic markers, expression of gene may validate as a prognostic factor in (EPTB). The diagnosis (EPTB) poses a special challenge, as it is often missed or misdiagnosed due to its atypical presentations and difficult to isolate *M tuberculosis (MTB)* due to the small number of organisms present at these sites. Subsequently the outcome of present study will reinforce possible use of *LTA4H* as biomarkers and the therapeutic utility for (EPTB). This study will be a step to decrease the analytical and therapeutic window to identify another risk factor *LTA4H* for EPTB. Leukotriene A4 hydroxylase (*LTA4H)*, an enzyme which changes LTA 4 to LTB4, controls the balance amongst the anti-inflammatory lipoxins and pro-inflammatory LTB4, with directly consequences in TB-driven inflammation. In humans and will spawn new ways to protection and enhance the wellbeing status of individuals and population groups. On RT-PCR, Extra Pulmonary Patients had lower expression of *LTA4H* compared to the controls. Correlation of biomarkers will reveal *LTA4H* level correlated with age, Gender Smoking, Clinical Parameter Serum Total Protein, BMI Height and TLC, Laboratory Parameter. On ELISA kit and follow as per manufacturer protocol. CEA562Ge 96 Tests Enzyme-linked Immunosorbent Assay Kit For Leukotriene B4 (*LTB4) LTB4* Protein level in Extra Pulmonary Patients, (EPTB) (2304.52pg/ml) had lower expression of gene *LTB4* compared to the controls (3096.142pg/mls) (P value = 0.0012).

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***Key words* : *LTA4H gene*, Real Time PCR, Extra Pulmonary Tuberculosis, ELISA.**

Tuberculosis (TB), caused by Bacillus *Mycobacterium tuberculosis*, is a few of the top 10 causes of mortality globally and the prominent cause of death from a single infectious agent (ranked higher than HIV/AIDS)[1]. *M tuberculosis* infects almost one-quarter of the worldwide inhabitants. However, among the one-quarter of the World-wide population infected by *Mycobacterium tuberculosis,* simply just about 10% growth to clinical disease [2]. Highly affected persons take the germs exclusive of communicating apparent infection for their complete life cycle, which suggests that host sensitivity is a significant probability component for the advancement of effective Tuberculosis following disease[3]. Numerous genetic components have been discovered in research of different sources to be valuable in tuberculosis[4,5]. LeukotrieneA4hydrolase (*LTA4H*) is a monomeric, cytosolic, zinc metalloenzyme which catalyses the Leukotriene B4 (*LTB4*) generation in amino acid metabolic route and standardizes the equilibrium of *LTB4* and *LXA4* generation[6]. This equilibrium can influence TNF production. TNF is an essential component which affects the kind of macrophage killing after *M tuberculosis* contamination. Macrophage caspase-mediated cell death can monitor the distribution of *M tuberculosis,* but macrophage mortification may improve the dispersion of *M*

Editor's Comment :

- These findings suggest the expression in the LTA4H gene might influence the sensitivity to Extra Pulmonary Tuberculosis and new potential genetic risk factors of Extra Pulmonary Tuberculosis. This study will be a step to reduce the diagnostics therapeutic window to other risk factors (LTA4H) to Extra Pulmonary Tuberculosis and will span to new ways to safeguard and improve the health status.

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tuberculosis. Therefore, here is an assumption that the activity of *LTA4H* can influence the development of Tuberculosis subsequently M *tuberculosis* contagion. Newly, as a contender gene participating in TB, the polymorphisms in *LTA4H* gene were investigated in a case management group study in a Vietnamese inhabitant[7]. Of the six individual nucleotide polymorphisms (SNPs) findings, two have being discovered to be substantially correlated with Tuberculosis. The identical 6 SNPs were also explored in a Russian inhabitant but nothing of them demonstrated considerable correlation with pulmonary tuberculosis[8]. Polymorphisms in the gene *LTA4H* might influence sensitivity to Extra Pulmonary Tuberculosis and shift the possibility of developing the infection in the Han population in the East China[9].

Materials nd Methods

Study Design : It is a case control study. The current study was performed on patients suffering from Extra Pulmonary Disease, fulfilling the inclusion & exclusion criteria. Patients were enrolled from the Respiratory Medicine Department, King George's Medical University (KGMU), Lucknow attending OPD. Authored notified authorization was carried from each subject before inclusion in the research. The research was endorsed by the official Ethics Committee (Registration no: ECR/262/Inst/up/2013/RR-16)-Ref.code:94th CMIIB-PhD/PI

EPTB Patients :

The investigational work was accomplished in the Departments of Biochemistry and Respiratory Medicine -KGMU. Lucknow.

Study Participants : Selection Criteria

A clinically EPTB subject was kept in case group and healthy subjects for control group. Inclusion and exclusion standards of both groups was as follows-

We enrolled a total of 274 EPTB patients effecting the inclusion and exclusion criteria from Outpatient and Indoor patient Department of Respiratory Medicine, Lucknow. Data were collected on a standardized questionnaire for each subject. This included demographic characteristics age and Gender, Clinical history (Case definitions), Past and family history, Anthropometric data. Notified agreement was taken from 274 patients or guardian.

Healthy Control : Age and Gender -matched had been selected. An only a healthy person was enrolled with not any history of Respiratory disease.

Collection of Blood Samples : Transferred Blood in Triazole vial (1:3 ratio; 1 ml blood and 3 ml of Triazole) for gene expression was stored at -80^{0}C till further use.

Diagnostic Category : The patients were confirmed as EPTB by difference diagnostic tools as X-ray, Microscopy, ultrasound, CT scan and others (Table 1) and also diagnosed and confirmed by the PPD and blood investigation (Table 2)The patients were believed distinct EPTB if along with essential criteria there were Acid Fast Bacilli (AFB) in CSF smear or culture, Gene-Xpert or PCR positive for AFB nucleic acid or demonstration of AFB in extra CNS Tuberculosis. Presence of essential and two supportive criteria was considered highly probable EPTB Post-PCR dissociation curves were utilized to validate the specificity of single target amplification. Expression of all genes was normalized to the expression of Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH), a housekeeping gene. The Cp value of gene is used for calculation of fold expression of gene. The 10 µl of sybergreen (Takkara), 1 micromolar forward and 1micromolar reverse primer, 1µl cDNA and 7 µl of water were used for amplification of 20 µl one well reaction. RT-PCR was performed using a Roche system (Light cycler 480;).

RNA Extraction and CDNA Synthesis :

Complete RNA was separated from EDTA blood samples using Triazole reagent (Invitrogen, Rockville, MD, USA). The dilution and reliability of the RNA have been determined by determining the absorbance at 260 and 280 nm by Spectro-photometer. Total RNA was having reverse transcription to c-DNA using a cDNA reverse transcription kit (Applied Bio system, USA) and amplified by Real-time PCR (RT- PCR) and the melting temperature (Tm) of primer was standardized by simple RT-PCR. RT-PCR was accomplished using

Table 1 — *Confirmation of EPTB patients*

Clinical diagnosis	Frequency	Percent
X-ray	40	29.2
Microscopy	32	23.4
Ultrasound	15	10.9
CT scan	13	9.5
Other	37	27.0
Total	137	100.0

Table 2 — *Clinical data of case (EPTB) case groups*

	Groups						p-value
	Cases		Controls		Total		
	N	%	N	%	N	%	
PPD test :							
Present	67	48.9%	0	0%	67	24.5%	<0.001
Absent	70	51.1%	137	100%	207	75.5%	
Blood investigation :							
Present	127	92.7%	0	0%	127	92.7%	NA
Absent	10	7.3%	0	0%	10	7.3%	

SYBR Green Super mix (MAKE) and Single-Color RT-PCR Recognition System. The quantity of template utilized in the PCR responses was cDNA corresponding to 200 ng reverse-transcribed total RNA. DNA polymerase was first triggered at 95°C for 3 minutes, denatured at 95°C for 30 seconds and annealed/ extended at 61°C for 30 seconds, for n cycles according to the manufacturer's protocol (REF). Manifestation of the maintenance gene GAPDH functioned as an inside positive control in each assay performed.

Quantification of Nucleic Acids :

Extracted RNA was evaluated and assessed for purity using the Nano Drop 2000C UV-Vis Spectrometer. The Nano Drop loading surface was cleaned and 1 µl of dH2O applied to initialize the Nano Drop 2000C Software (Nano Drop Technologies, Wilmington, USA). A second application of 1 µl dH2O was used to blank the Nano Drop 2000C software to register a zero value. 1 µl of RNA was utilized to the Nano Drop and the concentration was determined by the instrument in n g/µL units at 260nm wavelength and the veracity was evaluated by determining the ratio of absorbance at 260nm to the absorbance at 280nm wavelength. Ratios of absorbance at 260/280 nm and 260/230 nm were determined by the Nano Drop 2000C Software. A ratio of 1.8 – 2.0 is of pure RNA.

RNA Gel Electrophoresis :

Above eluted RNA samples of each BLOOD sample were equally diluted to make equal concentration of each RNA samples and were run on the 0.8% agarose gel along Ladder

Polymerase Chain Reaction (PCR) :

Specific sequences can be easily amplified using conventional PCR (using templates)[10]

Statistical Analysis :

Constant data were surmised as mean ±SD while categorical data in number and percentage. One way to analyse covariance (ANOVA) was done for the analysis the correlation between Demographic and *LTA4H* and *LTB4* Gene. Statistical Package for the Social Sciences (SPSS) software version 20.0 was used to analyze the data. Statistical significance was set as $p<0.05$.

Results

The demographic data were documented and calculated the deformities as represented in (EPTB) Case group. (Table 3). The demographic data of the participants: 137 cases representing out of 274 representing the case and 137 case representing as control group. Respondents <18 years male were 3(1.09%), female were 5 (1,82 %). Total no 8 (2.9%)

Table 3 — *The demographic data were recorded and calculated the deformities as represented in (EPTB) Case groups*

	SEX		
	Male	Female	Total
Age Intervals :			
<18 years	3 (1.9%)	5 (4.2%)	8 (2.9%)
18-35 years	82 (53.2%)	65 (54.2%)	147 (53.6%)
36-50 years	43 (27.9%)	34 (28.3%)	77 (28.1%)
51-65 years	26 (16.9%)	16 (13.3%)	42 (15.3%)
Total	154 (100.0%)	120 (100.0%)	274 (100.0%)

Applied χ^2 test for significance, χ^2 value=1.71; df (3); p-value=0.636

Respondents between 18 to 35 years male were 82 (53.2%), female were 65 (54.2%) and total no 147 (53.6%). Respondents between the 36-50 years male were 43(27.9%), female were 34(28.3%) and total number 77 (28.1%). Respondents between 51-65 years male were 26(16.9%), female were 16(13.3%) and total no. 46 (15.3). Applied χ^2 test for significance. χ^2 values=1.71; df (3); p-value=0. 636. There is gender difference to sample helping the significance of study. The distribution of the sample for Smoking type shows Current smoker 23(8.4%), Ex-smoker 18(6.6%), Passive smoker16(5.8%) and Non-smoker were 217(79.2%). The duration of smoking (yrs) was 20.72 and 11.36,no of Cigarette were 2.25 and 0.97 and pack years of the smoking were 21.94 and 0.97. Other distribution of Alcohol and Gutkkha chewer were present the Alcohol consumption present in 10 (7.3%),absent in 127(92.7%) and gutkkha chewing present in 17(13.7%),absent in 107(86.3%) (Table 4). Site and clinical diagnostic of Extra Pulmonary Tuberculosis (EPTB) in case representing that the participants belongs to the types of site in the Extra-pulmonary Tuberculosis for example in Abdominal 33 (24.1%) lymph node 21(15.3%) Pleural 32 (23.4%) Pots 7(5.1%) TBM 15(10.9%) Genitourinary 3(2.2%) Miliary 3(2.2%) Other 23(16.8%) (Table 5) Confirmation of

Table 4 — *Smoker, non-smoker and ex-smoker and Alcohol data of case and control groups*

		N	%
Smoking type :	Current smoker	23	8.4%
	Ex-smoker	18	6.6%
	Passive smoker	16	5.8%
	Non-smoker	217	79.2%
		Mean	**SD**
No of cigarette		2.25	0.97
Duration of smoking (years)		20.72	11.36
Pack years		21.94	12.27
		N	**%**
Alcohol	Present	10	7.3%
	Absent	127	92.7%
Gutkkha chewer	Present	17	13.7%
	Absent	107	86.3%

Table 5 — *Site and clinical diagnostic of Extra Pulmonary Tuberculosis (EPTB) in case*

Types of side	N	%
Abdominal	33	24.1%
Lymph node	21	15.3%
Pleural	32	23.4%
Pots	7	5.1%
TBM	15	10.9%
Genitourinary	3	2.2%
Miliary	3	2.2%
Other	23	16.8%
	137	100%

EPTB patients shows that the clinical diagnosis for the cases by the different method like X-Ray 40 (29.2) Microscopy 32(23.4) Ultrasound 15(10.9) CT scan 13(9.5) Other37(27.0) (Table 1) .

Correlation of Laboratory Parameter : lta4h gene the expression value of mean standard deviation and the median of case has mean .92, SD 1.27 and Median. 51 (Table 6) and the correlation of lta4h gene expression value in AGE, BMI Protein Haemoglobin tlc and the smoker (No of cigarette) and the correlation by the Spearman's rho is the distribution (Table 6) . lta4h gene Spearman's rho 1 and the significance p-value is nil of the 38 patients and the age Spearman's rho-0.175 significance 0.292 in 38 patients. BMI-0.241 p-value 0.145 in 38 patients. Protein 0.273 p-value 0.097 in 38 patients. Haemoglobin-0.259 p-value 0.116 in 38 patients. TLC (cumm) -0.342* p-value 0.036 in 38 patients. No. of cigarette -.678* p-value 0.022 in 11 patients. Clinical data of case (EPTB) case group shows the case and control group present Monteux test (PPD) test present case 67(48. 9%) control 0(.0%) Total no 67 (24.5%), absent 70 (51.1%) control the 137 total no 207(75.5%), significance is <0. 001. The blood investigation present in case 127(92.7%) and control 0 (0%) Total no 127 (92.7%), absent 10 (7.3%) control group 0(0%) Total no10 (7.3%) and there is no significance level (Table 2). The case and control group the applied the unpaired t test for the significance level of different factors as age, weight, height and BMI in cases mean SD age 33.09 and 12.85 control 41.83 and 11.72 total mean 37.46 and 13.03 the significance is<0.001 (Table 6) For the weight in mean 47.52 SD 6.74 and the control 161.28 SD 4.17 total mean 37.46 and significance i<0.001 (Table 6). For the height 162.68 SD 4.01 and the control. 60.88 SD 5.17 Total mean 111.78 SD 51.20 the significance level of <0.001(Table 6). For BMI mean 23.2 SD 1.60 control group 23.66 and SD 1.80 and the total mean 23.49 SD 1.71 for significance is 0.105 (Table 6).

Table 6 — *lta4h gene expression value*

	Mean	Standard Deviation	Median
lta4h gene expression value	0.92	1.27	0.51
Parameters	Spearman's rho	p-value	No of patients
lta4h gene expression value	1	-	38
AGE	-0.175	0.292	38
BMI	-0.241	0.145	38
Protein	0.273	0.097	38
Haemoglobin	-0.259	0.116	38
TLC (cumm)	-0.342*	0.036	38
No of cigarette	-0.678*	0.022	11

LTA4H Expression :

LTA4H mRNA expression evaluated by real time PCR using SYBR green method. The expression levels of LTA4H gene, were lower in patients than control (Fig 1). The above study the correlation of different parameter and *LTA4H* gene are found. *LTA4H* gene were considerably correlated with Age Sex, Medical history, Socio-economic status, Occupation and other clinical parameter We are associated with *LTA4H* mRNA expression. The expression levels of *LTA4H* gene with lower expression with case compered the control. Abdominal lymph node Pleural Genitourinary TBM, Miliary pots and other part of the tuberculosis. and other Extra Pulmonary Tuberculosis. These findings were suggested that Expression in the *LTA4H* gene might be influence the sensitivity to Extra Pulmonary Tuberculosis and a new potential genetic risk factor of Extra Pulmonary Tuberculosis. This study will be a step to reduce the diagnostic and therapeutic window to identify another risk factor (*LTA4H*) for Extra Pulmonary Tuberculosis and will spawn new ways to safeguard and improve the health status of individuals and population groups. On RT-PCR, Extra pulmonary Patients had lower expression of *LTA4H* compared to the controls. Correlation of biomarkers: *LTA4H* level correlated with Age, Sex Smoking, Protein, BMI TLC are the different level the correlation is found with significant of Extra Pulmonary Patients. Applied unpaired t test for significance.

Fig 1 — Error Bar diagram shows Lower expression of LTA4H in the patients with Extra Pulmonary (case) compared to controls

Discussion

An experiment was performed on animal model zebrafish and found susceptibility for *Mycobacterium marinum*, can result from either inadequate or excessive acute inflammation[7]. Researchers revealed the two distinct molecular routes to *Mycobacterial* susceptibility converging on dys regulated TNF levels: inadequate inflammation caused by excess lipoxins and hyper inflammation driven by excess *LTB4*. In humans, recognize a single nucleotide polymorphism (SNP) in the *LTA4H* promoter region that regulates its transcriptional activity. In tubercles meningitis, polymorphism was correlated together with inciting cell recruitment along with patient survival and response to adjunctive anti-inflammatory therapy. A study by[11] . and several additional findings have shown a similar effect in different diseases, single nucleotide polymorphisms in 5-lipoxygenase activating protein (ALOX5AP) and *LTA4H* genes were associated with *LTB4* over production in myocardial infarction susceptibility. A single study of India [12.] has evaluated the genetic contribution of Leukotriene variants with Coronary Artery Disease (CAD) and observed the association of these variants with plasma *LTB4* levels. Plasma LTB4 levels were measured in 150 subjects of each case and controls by *LTB4* Immunoassay. Plasma *LTB4* levels were higher in cases than in controls *LTB4* measured by ELISA and *LTA4H* mRNA expression evaluated by real time PCR using SYBR green method. The expression levels of *LTA4H* gene, TNF, IL-8 were higher in patients than. The researchers observed a promoter region SNP (rs17525495) and an intronic SNP (rs1978331) we are associated with *LTA4H* mRNA expression. We are evaluated the gene *LTA4H* mRNA expression evaluated by real time PCR using SYBR green method. The expression levels of *LTA4H* gene with lower expression with case compered the control and above study the correlation of different parameter are found. Finally, they concluded that *LTA4H* exhibit close association in subject with circulatory disease and might deliver incremental values for predicting cardiovascular risks, In the present study results of RT-PCR, revealed that Extra Pulmonary Patients had lower expression of *LTA4H* compared to the controls. Recent studies recommended extremely appropriate association of *LTA4H* gene polymorphisms along with various ethnicities and TB infection. Genomic display in zebrafish embryo and found a group of mutants hyper susceptible to *M marinum* infection[7]. Mutations in the *LTA4H* gene of zebrafish were presented heightened infectious growth and decreased TNF signalling. Mutations of the *LTA4H* gene reduced its expression and redirected

LTB4 synthesis along with production of the anti-inflammatory *LXA4.* Tobin and his co-workers were also tested whether heterozygosis at *LTA4H* protected against another mycobacterial disease in a different population in a different environment, *LTA4H* confers protection from development of severe disease among exposed persons. These outcomes recommend that conventional polymorphisms in the *LTA4HH* gene do not work any key function in sensitivity to clinical pulmonary tuberculosis. The contradictory results of these different studies are force to recognize *LTA4H* gene polymorphism in different ethnic groups as well as diseases. Due to this motive a recent study [13,9] was examined to the association of LTA4H polymorphisms with tuberculosis in a Han Chinese population of Eastern China. They were genotyped to the 5 SNPs (rs1978331, rs2247570, rs2540474, rs2660898, rs2660845) of LTA4H gene in 743 of Pulmonary Tuberculosis patients, 372 of Extra Pulmonary Tuberculosis patients and 888 of healthy controls persons. Genotyping of the SNPs was performed with the SNPlex Genotyping System (Applied Biosystems, USA). These findings were suggested that polymorphisms in the *LTA4H* gene may be influence the sensitivity to EPTB and a new potential genetic risk factor of EPTB. Polymorphisms were genotyped by real-time PCR using the TaqMan probes. They found neither rs17525495 nor rs1978331 and rs2660898 SNPs displayed significant association with Pulmonary tuberculosis. In tubercles meningitis, polymorphism was correlated with inflammatory cell recruitment all along with patient existence and response to adjunctive anti-inflammatory therapy[14,15,10]. With our best knowledge this is the primary study from India to address the *LTA4H* gene polymorphisms, its mRNA expression of present study with RT-PCR results in Extra pulmonary patients had lower expression of *LTA4H* gene to compared to the controls sample *LTA4H* level correlated with age, Gender Smoking, Serum Total Protein , SGOT, SGPT, Tubercular, Hydrocephalus. On ELISA, Extra Pulmonary Patients(2304.52pg/ml) had lower expression of LTB4 compared to the controls (3096.142pg/mls) (P value = 0.0012).

Conclusion

This study will explore the role of LTA4H gene and may be establish another candidate that influence the susceptibility to Extra Pulmonary Tuberculosis in the Northern population of India. This study will be the first

report on LTA4H gene Polymorphisms among North Indian tuberculosis patients and may suggest a new potential genetic risk factor of Extra Pulmonary Tuberculosis. Among various diagnostic markers, Expression of the plasma LTB4 protein may validate as a prognostic factor in Extra Pulmonary Tuberculosis, its mRNA expression and plasma LTB4 levels will depict that functional variant of LTA4H may modulate Tuberculosis by regulating LTB4 production. So, the level of pro-inflammatory marker LTB4 in plasma may highlighted towards a primary diagnosis of Tuberculosis. Subsequently the outcome of present study will reinforce possible use of LTA4H as biomarkers and also the therapeutic utility for Extra pulmonary Tuberculosis. This study will be a step to reduce the diagnostic and therapeutic window to identify.

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Original Article

An Observational Study Comparing the Adverse Effect Profiles of Sputnik V and Covaxin COVID-19 Vaccines in Adult General Population of Eastern India

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Aim : Currently no data is available on the safety profile of COVID-19 Vaccines like Covaxin and Sputnik V from Eastern India. Our aim was to evaluate the safety profiles of Covaxin and Sputnik V Vaccine in Eastern India.

Methods : 0.5 ml of Covaxin and Sputnik V given to 701 adults in a two-dose regimen at a private tertiary care Hospital, Kolkata, with the doses separated by 4-7 weeks in Covaxin and 3 weeks in Sputnik V. Data regarding local and systemic Adverse Event Following Immunizations (AEFIs) was collected 30 minutes after vaccination and also on the first- and seventh-day following vaccination after each dosage.

Results : Incidence of AEFI was 65% and 59% following the first dose of vaccination in Covaxin and Sputnik V groups, respectively. Incidence of AEFI was 83% and 70% after the second dose in Covaxin and Sputnik V groups. Pain in the injection site was the most common adverse effect. Body-ache, fever and tiredness were other systemic side effects. Adverse effects were noticeably more after the second dose. Over half of the reactions were mild in nature. Covaxin had a higher number of moderate adverse reactions after both doses. Adults with age >40 years, Co-morbidities, Hypertension and Diabetes had a smaller number of side effects following the first dose of vaccination. People with previous COVID-19 infections had noticeably fewer adverse effects after the second dose. Allergic adults were associated with more systemic side effects, whereas Hypertensive adults had less total AEFI.

Conclusion : Both Covaxin and Sputnik V had favorable safety profiles. Sputnik V vaccine had significantly fewer AEFIs compared to Covaxin. Age, co-morbidities, specifically hypertension, Diabetes, Allergy and previous history of COVID-19 infection, were important variables observed in the prevalence of side effects.

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Key words **: COVID-19 vaccine, AEFI, Safety, Covaxin,Sputnik V, Adverse effects, Side effects, India.**

Coronavirus 2019 (COVID-19) is a viral pneumonia like illness which is the cause of worldwide destruction of public health and economic instability. According to WHO, over 450 million people were affected Worldwide till date, with a death rate of 6 million[1].40 million people had been affected in India till date with a death rate of 0.5 million[2].

Editor's Comment :

- COVID-19 is a viral pneumonia like illness causing worldwide destruction of public health and economic instability.
- Vaccination is an effective way to curtail the spread of the disease and decrease mortality. This study investigates the adverse effect profiles of COVID-19 vaccines Covaxin and Sputnik in adult general population of Eastern India.

Currently, supportive measures, ie, oxygen, anticoagulant and intravenous steroids, are the cornerstone of COVID-19 treatment. For this reason, vaccination can be an effective way to curtail the spread of COVID-19 disease and decrease mortality. The urgent need for vaccination to prevent COVID-19 spread has spurred the development of different vaccines.

Though several vaccines are currently given permission for emergency use in India, only Covishield, Covaxin and, Sputnik V are being used for mass vaccination purpose[3]. Covishield was used for almost 85% of mass vaccination, whereas Covaxin and

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Sputnik V are applied for 12% and 3-4% of vaccination in India[4]. Covaxin and Sputnik V having the efficacy of 78% and 91.65%, respectively, are the most common vaccines used in India for mass-vaccination purpose[5,6]. Despite the enormous usage of both vaccines, sufficient data is not available regarding the comparative safety of these vaccines worldwide. Only one study is available which compares the adverse effects of both vaccines in health workers of Iran[7]. However, no study is available comparing the side effects of both vaccines in the adult general population. This is the first study that measures the side effects of both vaccines in the Indian population.

Materials and Methods

Our Prospective observational study was carried out at Peerless Hospital, Kolkata, from July 2021 to September 2021 after the approval of the Ethics Committee. Individuals over 18 years who consented to participate in the study were included. Positive COVID-19 patients were excluded from the study. Patients' demographic characteristics and incidence, type, pattern and severity of AEFI were collected. A 0.5ml dosage of Covaxin or Sputnik was injected intramuscularly at the deltoid in a two-dose regimen, with the doses separated by 4-7 weeks in Covaxin and 3 weeks in Sputnik. Data regarding AEFI after thirty minutes of vaccination were collected. Participants were contacted by phone after 24 hours following vaccination, as well as after each dosage on day 7. Individuals were especially questioned about local site symptoms such as pain, erythema, edema, soreness, and degree of physical activity limitation for safety analysis. They were also asked about systemic symptoms, including Fever, Headache, Nausea, Vomiting, Diarrhea, Rash, Chest tightness, Dyspnea, etc. Biochemical testing was not performed routinely on all vaccination recipients but was planned in the event of severe AEFI or AEFI persistence. Results were analysed using SPSS version 22. Descriptive statistics (Frequency and Percentage), Pearson's Chi-square test, Fisher's exact test, Mann-Whitney U test and logistic regression analysis were used. $p<0.05$ was considered statistically significant.

Results

716 adult individuals were screened for their first dose of vaccination. Among them, the first doses of Covaxin and Sputnik V were given to 519 and 182 individuals, respectively. 200 and 182 individuals were given the second dose of vaccine in Covaxin and Sputnik group, respectively. The mean age of individuals in Covaxin and Sputnik V group was 41 and 39 years, respectively. History of previous COVID-19 infection in Covaxin and Sputnik V group was 47% and 41%, respectively.36% and 27% individuals had co-morbidities in Covaxin and Sputnik groups, respectively (Table 1). Total incidence of adverse effect and systemic side effect were significantly more in both groups after the second dose of vaccination (Table 2). Local adverse effect, ie, pain in the injection site was the most common side effect observed in both groups after both doses of vaccination. Among systemic side effects, body ache was the most prevalent one after first and second dose of vaccination in both groups. Other common adverse effects were Tiredness and Fever. Nausea-vomiting was noticeably more after the second dose of vaccination in both groups. Additionally, Fever, Tiredness, Malaise, Cough, and Sneezing were more frequently observed after the second dose of vaccination in the Covaxin group. Loss of sleep was observed more frequently after the first dose of vaccination in Covaxin group. Sneezing, difficulty in urination, change in appetite and increased sleep were not observed in the Sputnik V group. Incidence and pattern of side effects were not significant after the first dose of vaccination in both groups. The total incidence of adverse effect and systemic side effect were significantly lower in Sputnik group compared to Covaxin group ($p<0.05$) after the second dose of vaccination (Table 3). Additionally, Cough, Diarrhea, Sneezing and tiredness were observed more frequently in Covaxin group after the second dose.

In MEDRA SOC classification, Gastrointestinal disorders and Respiratory-thoracic-mediastinal disorders were observed more frequently in Covaxin group after the first and second dose of vaccination,

Table 1 — *Demographic details of population receiving first and second dose of vaccination*

Demographic details	Covaxin group (n=519)	Sputnik V group (n=182)
Sex (Male)	243 (46.82%)	94 (51.65%)
Age	41.11± 14.93	38.47± 12.56
History of previous COVID infection	242 (46.63%)	74 (40.66%)
Co-morbidities	187 (36.03%)	49 (26.92%)
Arthritis	5 (0.96%)	0 (0%)
Thyroid disease	27 (5.20%)	3 (1.65%)
Hyper-lipoproteinemia	1 (0.19%)	4 (2.2%)
Asthma and COPD	4 (0.77%)	2 (1.1%)
Hypertension	84 (16.18%)	25 (13.74%)
Diabetes mellitus	57 (10.98%)	21 (11.54%)
Allergy	26 (12.15%)	6 (3.3%)
Liver disease	3 (0.58%)	1 (0.55%)
Chronic kidney disease	4 (0.77%)	0 (0%)
Others (cancer etc)	4 (0.77%)	1 (0.55%)
Concomitant medication	149 (28.71%)	40 (21.98%)

Table 2 — *Comparison of adverse effects in covaxin group after first and second dose of vaccination*

Adverse effects	First dose of vaccination (n=519)	Second dose of vaccination (n=200)	P value
Incidence of adverse effect	339 (65.32%)	166 (83%)	<0.001*
Incidence of systemic adverse effect	258 (49.71%)	145 (72.5%)	<0.001*
Fever	92(17.73%)	59 (29.5%)	0.001*
Body ache	163(31.41%)	72 (36%)	0.246
Pain in injection site	209(40.27%)	90 (45%)	0.251
Nausea and vomiting	6(1.16%)	18 (9%)	<0.001*
Malaise	29(5.59%)	25 (12.5%)	0.007*
Cough	5(0.96%)	10 (5%)	0.012*
Diarrhoea	25(4.82%)	13 (6.5%)	0.395
Sneezing	2(0.39%)	9 (4.5%)	0.006*
Urinary problem	1(0.19%)	1 (0.5%)	0.565
Skin-rash	10(1.93%)	10 (5%)	0.063
Loss of appetite	8(1.54%)	1 (0.5%)	0.157
Increase in appetite	2(0.39%)	4 (2%)	0.116
Loss of sleep	4(0.77%)	0 (0%)	0.045*
Increase in sleep	2(0.39%)	2 (1%)	0.415
Tiredness	59(11.37%)	52 (26%)	<0.001*

Comparison of adverse effects in sputnik V group after first and second dose of vaccination

Adverse effects	First dose of vaccination (n=182)	Second dose of vaccination (n=182)	P value
Incidence of adverse effect	108 (59.34%)	127 (69.78%)	0.036*
Incidence of systemic adverse effect	77 (42.31%)	107 (58.79%)	0.001*
Fever	36 (19.78%)	49 (26.92%)	0.106
Body ache	53 (29.12%)	67 (36.81%)	0.117
Pain in injection site	78 (42.86%)	79 (43.41%)	0.916
Nausea and vomiting	2 (1.1%)	17 (9.34%)	<0.001*
Malaise	12 (6.59%)	14 (7.69%)	0.684
Cough	1 (0.55%)	2 (1.1%)	0.562
Diarrhoea	4 (2.2%)	4 (2.2%)	1.000
Sneezing	0 (0%)	0 (0%)	NA
Urinary problem	0 (0%)	0 (0%)	NA
Skin-rash	1 (0.55%)	4 (2.2%)	0.176
Loss of Appetite	0 (0%)	0 (0%)	NA
Increase in appetite	0 (0%)	0 (0%)	NA
Loss of sleep	1 (0.55%)	1 (0.55%)	1.000
Increase in sleep	0 (0%)	0 (0%)	NA
Tiredness	18 (9.89%)	27 (14.84%)	0.151

*-p value<0.05,significant

respectively. In severity assessment, mild reactions were observed more frequently in Sputnik group after both first and second doses of vaccination. Adults with a history of comorbidity, hypertensive and diabetic adults had less adverse effects and systemic side effects after the first dose of vaccination. Additionally, adults >40 years had less adverse effects following the first dose. Furthermore, people with a history of allergy had more systemic side effects after the first dose. Also, more total systemic AEFIs were observed in allergic adults. People with the previous history of

Table 3 — *Comparison of adverse effects in both groups after first dose of vaccination*

Adverse effects	Covaxin group (n=519)	Sputnik V group(n=182)	P value
Incidence of adverse effect	339 (65.32%)	108 (59.34%)	0.149
Incidence of systemic adverse effect	258 (49.71%)	77 (42.31%)	0.085
Fever	92(17.73%)	36(19.78%)	0.537
Body ache	163(31.41%)	53(29.12%)	0.566
Pain in injection site	209(40.27%)	78(42.86%)	0.541
Nausea and vomiting	6(1.16%)	2(1.10%)	0.950
Malaise	29(5.59%)	12(6.59%)	0.619
Cough	5(0.96%)	1(0.55%)	0.602
Diarrhoea	25(4.82%)	4(2.20%)	0.127
Sneezing	2(0.39%)	0(0%)	0.402
Urinary problem	1(0.19%)	0(0%)	0.553
Skin-rash	10(1.93%)	1(0.55%)	0.198
Loss of Appetite	8(1.54%)	0(0%)	0.092
Increase in appetite	2(0.39%)	0(0%)	0.402
Loss of sleep	4(0.77%)	1 (0.55%)	0.760
Increase in sleep	2(0.39%)	0(0%)	0.402
Tiredness	59(11.37%)	18(9.89%)	0.583
MEDRA SOC classification	Total number of AEFI in first dose of vaccination (n=617)	Total number of AEFI in first dose of vaccination (n=206)	P value
General disorder and administration site conditions	389(63.05%)	144(69.9%)	0.067
Musculoskeletal and connective tissue disorder	163(26.42%)	53(25.73%)	0.845
Gastrointestinal disorders	41(6.65%)	6(2.91%)	0.016*
Skin and subcutaneous tissue disorders	10(1.62%)	1(0.49%)	0.106
Respiratory, thorasic, and mediastinal disorders	7(1.13%)	1(0.49%)	0.314
Psychiatric disorders	6(0.97%)	1(0.49%)	0.536
Renal and urinary disorders	1(0.16%)	0(0%)	0.317
Severity assessment (FDA)	Total number of AEFI in first dose of vaccination (n=617)	Total number of AEFI in first dose of vaccination (n=206)	P value
Grade 1(mild)	399 (64.67%)	156 (75.73%)	0.002*
Grade 2(moderate)	218 (35.33%)	50 (24.27%)	0.002*

Comparison of adverse effects in both groups after second dose of vaccination

Adverse effects	Covaxin group (n=200)	Sputnik V group (n=182)	P value
Incidence of adverse effect	166 (83%)	127 (69.78%)	0.002*
Incidence of systemic adverse effect	145 (72.5%)	107 (58.79%)	0.005*
Fever	59 (29.5%)	49 (26.92%)	0.576
Body ache	72 (36%)	67 (36.81%)	0.869
Pain in injection site	90 (45%)	79 (43.41%)	0.754
Nausea and vomiting	18 (9%)	17 (9.34%)	0.908
Malaise	25 (12.5%)	14 (7.69%)	0.121
Cough	10 (5%)	2 (1.1%)	0.029*

Diarrhoea	13 (6.5%)	4 (2.2%)	0.042*
Sneezing	9 (4.5%)	0 (0%)	0.004*
Urinary problem	1 (0.5%)	0 (0%)	0.339
Skin-rash	10 (5%)	4 (2.2%)	0.145
Loss Of Appetite	1 (0.5%)	0 (0%)	0.339
Increase in appetite	4 (2%)	0 (0%)	0.055
Loss of sleep	0 (0%)	1 (0.55%)	0.294
Increase in sleep	2 (1%)	0 (0%)	0.176
Tiredness	52 (26%)	27 (14.84%)	0.007*
MEDRA SOC classification	Total number of AEFI in second dose of vaccination (n=366)	Total number of AEFI in second dose of vaccination (n=264)	P value
General disorder and administration site conditions	226(61.75%)	169(64.02%)	0.561
Musculoskeletal and connective tissue disorder	72(19.67%)	67(25.38%)	0.092
Gastrointestinal disorders	36(9.84%)	21(7.95%)	0.409
Skin and subcutaneous tissue disorders	10(2.73%)	4(1.52%)	0.284
Respiratory, thorasic, and mediastinal disorders	19(5.19%)	2(0.76%)	0.001*
Psychiatric disorders	2(0.55%)	1(0.38%)	0.756
Renal and urinary disorders	1(0.27%)	0(0%)	0.317
Severity assessment (FDA)	Total number of AEFI in second dose of vaccination (n=366)	Total number of AEFI in second dose of vaccination (n=264)	P value
Grade 1(mild)	194 (53.01%)	183 (69.32%)	<0.001*
Grade 2(moderate)	172 (46.99%)	81 (30.68%)	<0.001*

*-p value<0.05,significant

COVID-19 infection had fewer number of adverse effects after the second dose of vaccination. Also, Hypertensive adults had less total AEFI in our study (Table 4).

Discussion

The COVID-19 is a Viral Respiratory disease and characterized by pneumonia-like illness. It is the cause of worldwide destruction of public health and economic instability. Supportive measures, ie, Oxygen, Steroid, and Anti-coagulants, are the cornerstone of treatment of this deadly disease. The vaccine is the most effective way to prevent the spread of COVID-19 disease. Though Covishield is the main Vaccine for Mass Vaccination purpose, Covaxin and Sputnik V are some of the commonly used vaccines in India[4].

We have observed that both Covaxin and Sputnik V vaccine have a favorable safety profile and are suitable for the Mass-Vaccination purpose. Incidence of AEFI was 65% and 59% following the first dose of vaccination in Covaxin and Sputnik V groups, respectively. Incidence of AEFI was 83% and 70% after the second dose in Covaxin and Sputnik V groups. According to the Zare's study in Iran[7], Covaxin and Sputnik V are associated with 92.9% and 81.9% side effects, respectively. Our study has also revealed that Sputnik V Vaccine had less number of side effects which is consistent with the Iranian study. Pain in the injection site was the most common adverse effect. Body-ache, fever and tiredness were other systemic side effects. According to Bharat Biotech's data on Covaxin, side effects reported are pain in the injection site, Fever, Malaise, Nausea-vomiting and rashes, consistent with our study[8]. In contrast, Headache is a common adverse effect in the manufacturer's fact-sheet though

Table 4 — *Relationship of AEFI with gender, age, previous history of COVID-19 and different co-morbidities (logistic regression analysis)*

AEFI	Adverse effect after first dose of vaccination	Systemic adverse effect after first dose of vaccination	Adverse effect after second dose of vaccination	Systemic adverse effect after second dose of vaccination	Total AEFI	Total systemic AEFI
Sex(male)	0.862	0.129	0.572	0.253	0.538	0.052
Age >40 years	0.017*	0.081	0.950	0.849	0.259	0.249
Previous history of COVID-19	0.180	0.171	0.037*	0.136	0.075	0.145
Co-morbidities	0.010*	0.005*	0.378	0.561	0.396	0.395
Arthritis	0.286	0.244	1.000	1.000	1.000	1.000
Thyroid disease	0.960	0.900	0.701	0.383	0.401	0.136
Hyper-lipoproteinemia	0.286	0.727	0.386	0.777	0.224	0.663
Asthma and COPD	0.144	0.483	0.683	0.980	0.254	0.576
Hypertension	<0.001*	<0.001*	0.097	0.100	0.037*	0.056
Diabetes mellitus	0.016*	0.002*	0.340	0.161	0.128	0.078
Allergy	0.130	0.002*	0.999	0.072	0.079	0.020*
Liver disease	0.999	0.929	0.999	0.704	0.999	0.992
Chronic kidney disease	0.643	0.302	0.999	0.999	0.999	0.999
Concomitant medication	0.424	0.079	0.786	0.990	0.952	0.958

*-p value<0.05,significant

not observed in our study. Tiredness is a common side effect of Covaxin observed after both first and second doses of vaccination in our study though not mentioned as a side effect in the manufacturer's fact-sheet. Other side effects, ie, Cough, Sneezing, Diarrhoea, Urinary difficulty, Changes in Appetite and Sleep, though few in number, are observed in our study, which are inconsistent with the manufacturer's fact-sheet. Side effects were noticeably more after the second dose. Over half of the reactions were mild in nature. Covaxin had a higher number of moderate adverse reactions after both doses. Adults with age >40 years, co-morbidities, Hypertension and Diabetes had a smaller number of adverse effects following the first dose of vaccination. According to Zare, younger adults are associated with more side effects which is consistent with our study[7]. On the contrary, people with previous COVID-19 infection have noticeably less adverse effects after second dose of vaccination. People with previous COVID-19 infections had noticeably fewer side effects after the second dose. Allergic adults were associated with more systemic adverse effects, whereas hypertensive adults had less total AEFI.

Small number of participants and short duration of follow-up were the limitations of the study. However, being the first real world study on the adverse event profiles of Covaxin and Sputnik vaccine in Eastern India this study adds to the evolving safety profile of COVID-19 vaccines in the country.

To conclude, both vaccines had a favorable safety profile and can be used for mass vaccination in India.

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Original Article

Serum Ferritin as a Marker of Psychiatric Disorders

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Serum ferritin, insulin resistance (HOMA), lipid profile and Body Mass Index (BMI) were studied on 44 patients of depression and 38 patients of schizophrenia before any specific treatment was initiated, and compared with 30 healthy controls. All studied schizophrenics showed normal BMI and serum ferritin was significantly decreased ($p<0.001$) whereas only about 57% of depressive patients had normal BMI and showed decrease in serum ferritin ($p<0.001$), and rest of the depressive patients had significantly raised BMI ($p<0.001$) as well as raised serum ferritin level ($p<0.001$). Depressive patients with raised ferritin level had significantly raised insulin resistance ($p<0.001$) along with raised serum triglyceride ($p<0.007$). Serum total cholesterol was increased and HDL cholesterol was decreased in both the conditions.

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Key words **: Ferritin, Insulin resistance, Depression, Schizophrenia.**

Depression and schizophrenia are two important psychological disorders in our society. Both the conditions have identifiable biochemical abnormalities of specific neurotransmitters. Nutrition also plays a role in the genesis of these two diseases. It is well established that vitamin B12, folic acid, niacin and vitamin C deficiencies can result in mood disorder[1]. Patients affected by iron deficiency anemia show many mood and behavioral signs and symptoms similar to depressed individual, many of which signs and symptoms appear in the initial stage of iron deficiency (dropped serum ferritin level) before the onset of frank anemia[2].

Data from third National Health and Nutrition Examination Survey (NHNES 3), 1988-1994 indicated that iron deficiency without anemia occurred up to 11% of women (most often pre-menopausal) and 4% of men[3]. Significant decrease in ferritin level in schizophrenic patients has been reported[4]. Alterations in iron metabolism in patients with depression have also been reported in several studies[5-7], whereas Baune B T, *et al* (2006) found no such association[8]. There are reports that depression is frequently linked with insulin resistance[5,9-11] and serum ferritin can be a marker for insulin resistance syndrome[5].

Editor's Comment :

- Psychiatric diseases (Depression & Schizophrenia) may be catagorised in two groups - (a) Low ferritin group. (b) High ferritin group.
- Patients witrh high ferritin group may develop insulin resistance syndrome (Metabolic syndrome) in the long run.
- Serum ferritin may be used as routine parameter for management of those diseases.

The present hospital based case control study was conducted on patients of depression and schizophrenia, compared to control to examine serum ferritin level, insulin resistance (HOMA) and lipid profiles and to find correlation among them in either of these conditions.

Materials and Methods

The present study was carried out during 2008 to 2010 at IPGME&R and BIN, Kolkata in the department of Biochemistry & Department of Psychiatry. Forty four patients of depression and 38 patients of schizophrenia, attending Psychiatric OPD were selected for the study. The patients were selected by criteria given in Diagnostic & Statistical Manual (DSM-4)[12] of mental disorder. The patients were considered for study at their first visit before starting of drug therapy. Thirty healthy individuals without any psychiatric

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disorder were chosen as controls.

Exclusion criteria :

Patients having hemoglobin less than 10gm%, positive CRP, history of taking drugs such as β-blocker, calcium channel blocker and anticonvulsant were excluded. Patients with known diabetes mellitus, coronary heart disease, hematological diseases, liver and thyroid disorders, alcoholism and mal-absorption were also excluded from this study.

Ethical committee of IPGME&R endorsed the study protocol.

Fasting blood samples were collected from the patients and healthy controls. Biochemical parameters, such as fasting plasma glucose, serum insulin, ferritin and lipid profile were done for this study. Serum urea, creatinine, TSH and CRP were done to exclude the conditions under exclusion criteria.

Estimation of Serum Ferritin :

Serum ferritin was estimated by immunoenzymatic sequential assay using ELISA microwells[13].

Estimation of Serum Insulin:

Monobind Insulin Microplate ELISA test was used for the quantitative determination of serum Insulin level[14].

Estimation of Plasma Glucose:

Plasma glucose estimation was done by Glucose Oxidase-Peroxidase method[15].

Estimation of Serum Lipid Profile :

Serum Cholesterol was estimated by Cholesterol Oxidase / PAP method[16]. Serum Triglyceride was estimated by Glycerol Phosphate Oxidase /PAP method[17]. Estimation of HDL cholesterol (Direct) was done by enzymatic method[18].

Estimation of serum urea, creatinine, TSH and CRP (to fulfill the exclusion criteria)

Serum urea and serum creatinine were estimated by Berthelot method and Modified Jaffe's method respectively[19,20]. Serum TSH was estimated by Enzyme Immuno Assay[21]. CRP was estimated by Latex agglutination immunoassay with monoclonal antibody[22].

BMI of the patients were also considered as demographic covariate. It is calculated as follows[23].

$$\mathrm{BMI} = \frac{\mathrm{Weight}\ (Kg)}{[Height(m)]2}$$

Insulin resistance was calculated as HOMA- IR[24].

$$\text{HOMA- IR} = \frac{\text{Fastingplasmaglucose(mg/dl)X FastingInsulin}(\mu IU/ml)}{405}$$

Statistical analyses :

Statistical analyses of data were carried out using SPSS software-version 16. Kruskal Wallis test was employed for comparison of statistical parameters among the groups. Correlation analysis within the groups of depressive patients has been done by Spearman's ranked correlation analysis. Criteria for rejection of null were fixed at the level of 95% confidence.

Results

On analysis it was observed that about 57% of depressive patient showed normal BMI and 43.18% raised BMI in respect to control. We categorized depressive patients into two groups: Group 1 with normal BMI and Group 2 with raised BMI. All schizophrenic patients of this study showed normal BMI in respect to control. Plasma glucose was increased more than control in depression (p value <0.021) and schizophrenia (p value <0.02; Table 1). Basal insulin concentration was increased significantly in Group-2 depression patients (p value < 0.001), but decreased in both Group 1 depression and schizophrenia. In spite of increased basal insulin concentration Group 2 depression patients showed more fasting plasma glucose level than others. So there is a tendency for development of insulin resistance in Group 2 depression as reflected in HOMA-IR value, which was significantly increased in Group 2 depression (p value <0.001). But HOMA-IR value was normal in patients of schizophrenia and Group 1 depression. Serum triglyceride was significantly increased (p value <0.007) in respect to control in Group 2 depression along with fall of HDL cholesterol (p value < 0.005). In this study serum total cholesterol was increased both in depression and schizophrenia in respect to control (p value <0.001 & <0.002 respectively).

Serum ferritin level was significantly decreased in patients of schizophrenia (p value < 0.001), but in case of depression, about 57% of patients (Group 1) showed decreased ferritin whereas 43.18% (Group 2) had increased ferritin level (p value <0.001 & <0.001 respectively) in respect to control (Table 1). In Group 2 depressive patients, serum ferritin level was positively correlated with HOMA-IR (Fig 1; r = 0.98, p<0.001) and also positively correlated with BMI (Fig 2; r = 0.527, p<0.01). Thus irrespective of type of disease, the group of patients having normal BMI showed decreased ferritn with normal insulin resistance and those patients having increased BMI had significantly increased serum ferritin and raised insulin resistance.

Discussion

Vahdat Shariatpanaahi M (2006) reported that there is alteration of iron metabolism in depression. Kuloglu *et al* (2003) observed low iron status in schizophrenic patients. Our observations corroborate these studies in both depression and schizophrenia. According to Sung-Wan Kim *et al*, (2018) study, Iron deficiency may affect dopaminergic transmission in the brain. This iron-dopamine interaction might therefore contribute towards development of symptoms in patients with schizophrenia[25]. Fernandez-Real *et al* (1998) reported serum ferritin to be a marker of insulin resistance syndrome[5]. Ashwan Abdulzahra Hashim (2020) showed in his study that there is a strong relationship between the level of serum ferritin and depression with inverse correlation[26]. One study by Hea Shoon Lee1 and Eunmi Park (2019) provided evidence of existing correlation between ferritin and depression with obesity[27]. In the present study 43.18% of depression cases had raised HOMA-IR and increased BMI (p value <0.001) but the rest of the cases had normal level (Table 1) in respect to control. The depressive patients with raised insulin resistance had also raised ferritin level compared to the other group. Serum ferritin is positively correlated with HOMA-IR (r = 0.98, p value <0.001, Fig 1). The lipid profile was also altered with increased triglyceride and total cholesterol and decreased HDL cholesterol in this group indicating that this group has a tendency to develop metabolic syndrome in future. It is not clear why a part of depressive patients had increased ferritin and insulin resistance and others were free from these changes. Probably this change is related to higher BMI of these patients. Though the sample size was small, this limitation may lead to type 2 error, which might have underestimated the difference from the control population, so the magnitude of the deviation from null is actually more and thus the chance of overestimation of the problem is less. However, the power of the study needs to be increased for better conclusion.

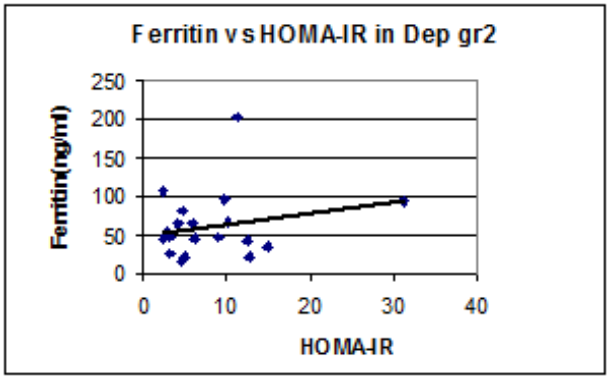

Fig 1 — Correlation of Ferritin and HOMA-IR in Depressive patients (Gr.-2) r = 0.980 (p value <0.001)

Ferritin level was rather decreased than control in schizophrenic cases. No significant changes in HOMA-IR and lipid profile except serum total cholesterol changes in schizophrenic patients was observed in this study indicating that these schizophrenic patients have less chance of developing metabolic syndrome.

It has been observed in previous studies that serum ferritin level is correlated positively with insulin resistance syndrome[9-11]. Our study partially agrees to these findings. Serum ferritin is also correlated with various indices of adiposity[28]. The mechanisms of such an association have not been identified, and it has been hypothesized that the hyperinsulinemia of the metabolic syndrome could be related to an accumulation of iron in the liver[29]. The precise mechanisms underlying the crosstalk between iron

Table 1 — *Biochemical parameters in patients of Group 1 Depression, Group 2 Depression (with Increased BMI in respect to Control) and schizophrenia*

Parameters	Control N =30		Depression (Gr-1) N = 26			Depression (Gr-2) with Increased BMI (N = 18)			Schizophrenia N = 38		
	Mean ± SD	SEM	Mean ± SD	SEM	P value	Mean ± SD	SEM	P value	Mean ± SD	SEM	P value
Plasma Glucose (mg/dl)	84.4±11.7	2.1	92.64±9.69	1.93	< 0.006	120.05±61.12	14.02	< 0.021	93.18±19.9	3.2	<0.02
Serum Insulin (mIU/ml)	7.99±2.17	0.39	4.85±2.91	0.58	< 0.001	26.24±13.47	3.09	< 0.001	5.01±4.2	0.68	<0.001
Serum Ferritin (ng/ml)	66.21±23.91	4.3	36.80±26.66	5.33	< 0.001	96.21±29.92	6.86	< 0.001	31.16±23.14	3.8	<0.001
Serum Triglyceride (mg/dl)	124.9±36.22	6.6	151.72±72.27	14.45	< 0.101	168.53±58.29	13.37	< 0.007	111.63±51.2	8.41	<0.020
Serum total Cholesterol (mg/dl)	143.73±21.8	3.9	186.86±35.96	7.19	< 0.001	197.98±41.23	9.45	< 0.001	171.76±45.7	7.5	<0.002
Serum HDL Cholesterol (mg/dl)	48.86±10.7	1.96	42.09±16.12	3.22	< 0.080	40.31±9.35	2.14	< 0.005	38.75±14.1	2.3	<0.001
HOMA IR	1.69±0.6	0.1	1.09±0.62	0.12	< 0.001	8.08±6.72	1.54	< 0.001	1.21±1.14	0.18	<0.03
BMI (kg/mt^2)	22.38±1.9	0.34	23.02±1.43	0.68	< 0.068	28.93±2.8	0.64	< 0.001	22.91±2.4	0.39	<0.322

stores reflected in hyperferritinemia and the development of insulin resistance remain un-clarified. Elevated ferritin levels may, in concert with other pathogenic factors, play a causal role in the development of impaired beta cell function and decreased insulin sensitivity. Iron mediates oxidative stress[30], and oxidative stress has many deleterious effects[31]. Iron overload has been shown to result in disturbed metabolic activity of the liver as well as skeletal muscle[32] together supporting a role of ferritin in insulin resistance. Increased iron reserve in the liver are postulated to induce liver-mediated insulin resistance with a reduced ability of insulin to suppress hepatic glucose production. Increased iron stores in the liver are postulated to induce liver-mediated insulin resistance with a reduced stability of insulin to suppress hepatic glucose production. Fernandez-Real *et al* (1998) considered that over expression of ferritin probably represents adaptive adiposites response to iron induced oxidative stress resulting in a postiive association between the serum ferritin concentration and the amount of fat tissue in the body[5] as shown by increased BMI in our study. The depression patients, particularly with raised BMI, thus diagnosed by DSM scale should be investigated for serum ferritin level to exclude insulin resistance syndrome. Decreased serum ferritin may also be utilised as a marker of schizophrenia. Ferritin is a major iron storage protein and plays a key role in iron metabolism[33,34]. Serum ferritin concentration provides an indirect estimation of body iron store. Data in men and non-pregnant women had shown that elevated serum ferritin was significantly associated with several cardiovascular disease factors[35]. Positive correlation between mildly increased serum ferritin concentration and indices of insulin resistance in both healthy subject and patient of type-2 diabetes mellitus have been reported[36,37]. Iron plays an important role as cofactor for some enzymes concerned with formation of different

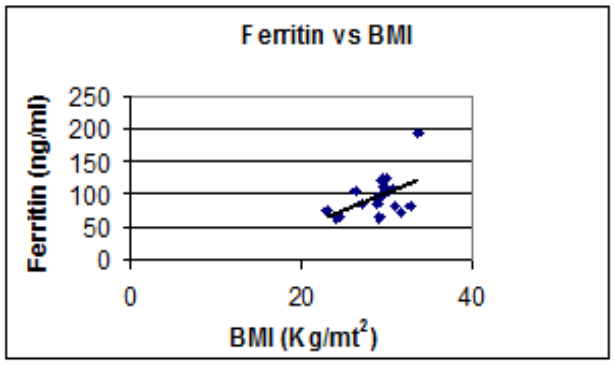

Fig 2 — Correlation of Ferritin and BMI in Depressive patients (Gr.-2) r=0.527 (p value <0.010)

neurotransmitters of brain, some of which are observed to be decreased in schizophrenia. Poor iron status therefore may play a contributing role in the genesis as well as progression of schizophrenia[4].

Despite significant research effort, diagnosis and evaluation of treatment of these psychiatric disorders are still based solely on relatively subjective assessment of symptoms. The search for peripheral markers for psychiatric disorders has been under way for many years but inspite of such efforts a non-invasive blood based test, that can be used for diagnosis and management still remains elusive. Measurement of serum ferritin concentration may be highly useful, non-invasive and cost-effective test for schizophrenia and insulin resistance syndrome in patients diagnosed as cases of depression.

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Original Article

Association between Stress Depression Anxiety and Coping Styles among Indian University Students during COVID-19 Outbreak

Priscilla Das[1], Saravana Kumar[2], Ramasamy Chidambaram[3]

Introduction : Psychiatric illnesses such as Depression and Anxiety can have a substantial impact on one's mental health. Depression is the most common psychiatric condition diagnosed among students.

Objectives : To find out the association of factors which are linked to Stress, Depression, Anxiety and coping styles among Indian University students during COVID-19 outbreak.

Methods : A self-administered questionnaire consisting of socio-demographic, DASS-21 and Brief-COPE inventory were used.

Results : The study comprised a total of 201 University students ranging in age from 17 to 36 years old. Female students (n=150) were the most common responses, followed by male students (n=51). Depression, anxiety and stress correlated with active coping, planning, positive reframing, acceptance, humor, emotional support, instrumental support, self-distraction, denial, venting, substance use, behavioral disengagement, self-blame and religion.

Conclusion : Venting, behavioural disengagement and self-blame are all examples of maladaptive coping techniques that have a significant impact on University students' Stress, Anxiety and Depression levels. This research will provide a better understanding of the underlying influence of coping methods on Stress, Depression, and Anxiety among university students during the COVID-19 outbreak, enabling for early intervention and improved outcomes.

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***Key words* : Psychiatric disorders, Stress, Depression, Anxiety, Student, Coping styles.**

The COVID-19 pandemic has been shown to have negative Psychological impacts on the populations[1,2]. Depression and Anxiety, for example, can have a substantial impact on a person's overall health[3,4]. According to previous studies, children with high levels of Depression and Anxiety have trouble in learning, memorising and achieving good grades[5,6]. Problem-focused coping (active coping, planning, and the use of instrumental support), emotionally focused coping (emotional support, positive reframing and religion), Adaptive coping (acceptance, humour) and Maladaptive coping (self-distraction, denial, substance use, behavioural disengagement, venting, and self-blame) are all assessable[7]. Students with low psychosocial characteristics, in particular, are more prone to suffer emotional discomfort and engage in these maladaptive behaviours. Long-term student who were optimistic experienced reduced levels of melancholy and anxiety, as well as less study-related problems[8,9].

Editor's Comment :

- The COVID-19 pandemic has been proven to have detrimental psychological effects among the population.
- Better coping styles can help to lessen depression, anxiety, and stress among the students during COVID-19 pandemic.
- Awareness on various coping styles which are associated with depression, anxiety and stress will give insight to overcome this COVID-19 outbreak situation more effectively among the students.

Despite the fact that college is the most enjoyable time of a person's life, they need work on their coping skills in order to overcome Depression and worry. The effectiveness of treatment will be reduced if depression and anxiety are left untreated and no effort is made to develop their overall coping mechanisms. There has been no research into the Stress, Depression, and Anxiety experienced by Malaysian university students during the COVID-19 outbreak in terms of coping mechanisms. The primary goal of the study is to determine how common stress, depression, and Anxiety are among University students, as well as their coping mechanisms and associated factors.

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Methodology

Objectives :

To find out the association of factors which are linked to Stress, Depression, Anxiety and coping styles among Indian university students during COVID-19 outbreak.

Materials and Methodology :

These are the list of questionnaires used in this study:

(a) Socio-demographic questionnaires
(b) Brief cope
(d) DASS-21 questionnaire

Study design :

Cross-sectional studies.

Study duration :

Two years.

Inclusion criteria :

The participant is chosen based on four primary inclusion criteria. To participate, students must first be enrolled at a University. Second, the person must be at least eighteen years old. Participants in the study must also be able to converse in English. Fourth, the interviewee must be qualified to take part in the conversation.

Sampling method :

Universal sampling.

Data collection technique :

Students are given an online form with three sections: socio-demographic surveys, DASS questionnaires and brief-cope questionnaires. The completed forms were gathered and reviewed for the study.

Questionnaires :

Socio-demographic questionnaires :

Students' age, gender, race, religion, marital status, education level, occupation, socio-economic position, and family members will be assessed using socio-demographic questionnaires.

Brief COPE :

The Brief COPE questionnaire's 14 coping styles categories are grouped into 14 domains. On a scale of 2 to 8, coping styles were rated. The questionnaire has a good level of validity and reliability. To score scoring strategies, the two components on each scale will be averaged (all scales ranged from 2 to 8). Validity and reliability of the brief COPE questionnaire are satisfactory. The Brief COPE has high validity and reliability among Malaysians in both English and Malay. The scale's internal consistency ranged from 0.25 to 1.00, and the Intraclass Correlation coefficient ranged from 0.05 to 1.00. From 0 to 0.53, the sensitivity was increased[10].

Results

The study comprised a total of 201 University students ranging in age from 17 to 36 years old. Female students (n=150) were the most common responses, followed by male students (n=51)(Table 1).

Table 1 — *Summarises the socio-demographic profile of the students*

	Frequency	Percentage(%)
Gender :		
Female	150	74.6
Male	51	25.4
Total	**201**	**100**
Religion :		
Buddhist	1	0.5
Christian	19	9.5
Hindu	166	82.6
Jain	1	0.5
Muslim	12	6
No religion	2	1
Total	**201**	**100**
Education level :		
Bachelor	185	92
Diploma	1	0.5
Foundation	9	4.5
Master	3	1.5
PhD	3	1.5
Total	**201**	**100**
Study Mode :		
Full-time	195	97
Part-time	6	3
Total	**201**	**100**
University/college :		
Private College	38	18.9
Private University	108	53.7
Public College	22	10.9
Public University	33	16.4
Total	**201**	**100**
AMET	1	0.5
Anna University	1	0.5
Annamalai University	21	10.5
Bharathiar University	1	0.5
Cuddalore Government Dental College	16	8
Indhiragandhi Dental College	1	0.5
Indira Gandhi Institute of Dental Science	74	36.8
KSR college	2	1
KSR Institute of Dental College Tiruchengodu	1	0.5
KSR Institute of Dental Science and Research	3	1.5
Madras Christian College	1	0.5
Mahatma Gandhi Medical College and Hospital	2	1
Mahatma Gandhi Medical College and Research Institute	4	2.0
MGR University	9	4.5
Prist University Pondicherry	1	0.5
Puducherry	5	2.5

	Frequency	Percentage(%)
Rajah Muthiah Dental College	11	5.5
Rajah Muthiah Dental College and Hospital	3	1.5
Rajah Muthiah Dental College, Annamalai University	1	0.5
Shri Krishnaswamy College for Women	1	0.5
Sies College of Arts Science and Commerce	1	0.5
Sri Balaji Vidyapeeth	19	9.5
Sri Ramachandra University	1	0.5
SRM	1	0.5
SSN College of Engineering	1	0.5
Tamil Nadu	2	1
Thanjavur	1	0.5
Vels University	1	0.5
Total	**201**	**100**
Rural	52	25.9
Urban	136	67.7
Total	**201**	**100**
Not Working	192	95.5
Working	9	4.5
Total	**201**	**100**
Marital status :		
Married	2	1
Single	199	99
Total	**201**	**100**

Depression correlated with active coping (r=0.272, p=0.000), planning (0.349, p=0.000), positive reframing (r=0.282, p=0.000), acceptance (r=0.399, p=0.000), humor (r=0.322, p=0.000), emotional support (r=0.262, p=0.000), instrumental support (r=0.204, p=0.004), self-distraction (r=0.349, p=0.000), denial (r=0.309, p=0.000), venting (r=0.448, p=0.000), substance use (r=0.149, p=0.035), behavioral disengagement (r=0.491, p=0.000), self-blame (r=0.509, p=0.000) and religion (r=0.253, p=0.000).

Anxiety correlated with active coping (r=0.284, p=0.000), planning (0.368, p=0.000), positive reframing (r=0.269, p=0.000), acceptance (r=0.414, p=0.000), humor (r=0.361, p=0.000), emotional support (r=0.281, p=0.000), instrumental support (r=0.240, p=0.001), self-distraction (r=0.352, p=0.000), denial (r=0.406, p=0.000), venting (r=0.454, p=0.000), substance use (r=0.163, p=0.021), behavioral disengagement (r=0.456, p=0.000), self-blame (r=0.543, p=0.000) and religion (r=0.250, p=0.000).

Stress correlated with active coping (r=0.312, p=0.000), planning (0.415, p=0.000), positive reframing (r=0.303, p=0.000), acceptance (r=0.422, p=0.000), humor (r=0.359, p=0.000), emotional support (r=0.308, p=0.000), instrumental support (r=0.269, p=0.000), self-distraction (r=0.411, p=0.000), denial (r=0.375, p=0.000), venting (r=0.479, p=0.000), substance use (r=0.143, p=0.043), behavioral disengagement (r=0.483, p=0.000), self-blame (r=0.570, p=0.000) and religion (r=0.213, p=0.002).

Discussion

According to a poll of Undergraduate students at Malaysian Public Universities, 64.6 percent of first-year students suffer from anxiety, 32.1 percent from depression, and 29.2 percent from Stress. Four factors have been identified as contributing to Depression: gender, age, educational major, and employment. Anxiety is associated to the mother's education major, but stress is linked to her income and work. Depression, Anxiety and Stress have all been linked to parental education. Students' academic performance is commonly harmed by Psychological diseases, and special care should be provided to them in order to improve their overall mental health. Depression, Anxiety and Stress can all be alleviated with better coping techniques[11].

Depression, Anxiety and Stress were shown to be more prevalent in students under the age of 19. (DAS). The DAS level decreased as people got older. Female students and those who resided in the dorms had a high rate of morbidity. Due to their analytical mind and introversion behaviour, students with a higher degree of DAS had lower physical, mental, social and spiritual scores but a higher emotional score. Students who live in joint households had a lower risk of Depression (23.6 percent) than students who live in nuclear homes because they find it harder to communicate their opinions with their parents (76.4 percent)[12].

Academic overload, such as test schedules, was a cause of Stress for students, with 69.7% expressing Depression and 94.4 percent expressing Anxiety. Due to their rigorous curriculum, students rarely engage in recreational activities, according to the report. It's worth mentioning that students in higher socio-economic categories were more depressed than those in lower socio-economic groups. In order to resolve the problem, the psychological component of the problem should be monitored in the University's health centre, according to the study. To aid in the development of students, the mentorship programme should be improved[12].

Students utilised adaptive coping techniques such as religious coping (score (SD): 6.02 (1.65); positive reframing (score (SD): 5.75 (1.62); planning (score (SD): 5.66 (1.63); active coping (score (SD): 5.62 (1.64), according to another study. Self-distraction was common among the students with a score (SD) of 5.51 (1.55), venting was popular with a score (SD) of 4.75 (1.60) and self-blame was common with a score (SD) of 4.62 (1.67). Male students are more likely than female students to be depressed. Students aged 22 were found to be more likely to suffer from Depression[11].

Religion, ranting, humour, denial, substance abuse, and behavioural disengagement have all been related to Depression as coping techniques. Meanwhile, humour, substance abuse, and behavioural disengagement have all been linked to Anxiety. Stress is associated to instrumental support, ranting, humour, denial, substance addiction and behavioural disengagement coping strategies. Students entering their first semester face various challenges. The unfamiliar environment, as well as academic pressures such as tests, final exams, and assignments, could jeopardise their ability to cope with their psychological challenges. Early detection and intervention among students, according to the research, can help students manage with depression, anxiety, and stress by teaching them suitable coping skills[11]. This research backs up the current study's findings, which show that depression highly correlated with self-blame, behavioral disengagement, and venting.

Meanwhile the anxiety and stress highly associated with behavioral disengagement and self-blame in the current study. Students have indicated that University life is more stressful than other phases of their lives. In research, effective coping mechanisms have been demonstrated to reduce stress levels among university Students[13]. Only a few research involving Malaysian university Students have been conducted[14,15]. while the majority of investigations have been conducted on western populations[13]. Stress levels among University students are influenced by a variety of factors, including cultural variations and age groups. Surviving throughout the study period is difficult and students may get more stressed as a result[16]. As students graduate, their Stress level is greatly influenced by their work prospects[14], as well as looking for internships and jobs[15]. To help students cope with Stress, extracurricular activities such as athletics should be promoted at the institution[13].

Research of 376 Medical and Medical sciences Students was done by the International Medicine School, Management and Science University. In 2009, the data was gathered in the middle of the semester. 46.3 percent of students indicated they were under too much or some Stress, followed by 47.6 percent who said they were under a little amount of Stress, and only 6.1 percent who claimed they were not under any Stress. When compared to non-smokers, smoking was found to be a significant factor in Stress (71.4%) (OR = 3.2, 95 percent confidence interval 1.5-7.0, P = 0.002). (43,7%)[17].

Planning, acceptance and positive reframing are all part of active coping, which entails taking action to ease a stressful situation. Among the avoidant strategies include denial, behavioural disengagement, ranting and humour coping techniques[7]. In the Klang Valley, the role of mindfulness as a mediator in Malaysian University Students' academic stress and self-regulation was investigated. Exams and faculty work were found to be the most common sources of student academic Stress in the survey. Controlling negative emotions, attitudes and behaviours might help students improve their academic rankings by increasing general awareness[18]. Lecturers at Universities, career counselling centres, and administrators all have a part in reducing student stress. Throughout the academic year, workshops on how to cope with stress should be held, and University Counsellors should take a more proactive approach to addressing concerns. These techniques may aid students in improving their academic performance by lowering the negative impacts of stress, such as bad health[17].

Conclusion

Venting, behavioural disengagement and self-blame are all examples of maladaptive coping techniques that have a significant impact on University Students' stress, Anxiety and Depression levels. This study provide a better knowledge of the role of coping methods, stress, Depression and Anxiety among University Students, enabling for early intervention and improvement of overall Mental Health problems.

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Review Article

Insights into Conflicts and Harmony in Doctor Patient Relationship through Transactional Analysis

Arun N Bhatt[1], Marina Rajan Joseph[2]

Doctor Patient Relationship (DPR) in India seems to be deteriorating. Remedial measures are incoherent compared to the multitude of factors associated. Transactional Analysis (TA) is a Social Psychology Theory and practice appropriate to analyse changing paradigms of DPR. TA shows that traditional stable DPR model was symbiosis inappropriate for modern era. Current DPR model is game relationship occurring due to failed attempts at symbiosis. Contractual relationship is a stable model of DPR appropriate for modern era and medical fraternity shall work towards bringing a paradigm shift in a coherent manner. TA may be one of the systems that offers models and tools useful for a paradigm shift.

[*J Indian Med Assoc* 2022; **120(8):** 55-8]

Key words **: Doctor Patient Relationship, Patient-clinician Conflict, Healthcare Violence, Worker safety in hospitals, Transactional Analysis.**

Medical fraternity in India is grappled with deteriorating Doctor-Patient Relationship (DPR). There have been reports of violence against doctors[1]. The scenario may be attributed to a number of factors such as deficiencies in healthcare delivery system, inadequate doctor-patient ratio, increasing awareness and easy access to information, consumer protection act, cost of medical education, corruption, inequity, technological development in medicine, growth in health insurance and workplace factors in hospitals[2]. Medical fraternity responded to increasing violence through emphasising communication skills in medical education, through legal course and even by hiring security personnel[2-4]. Remedial measures need to be multi-pronged considering the web of causation involved. Analysis of psychodynamics of doctor-patient relationship would give insights useful to direct course of action at various levels.

Transactional Analysis (TA) is a Social Psychology Theory developed by Eric Berne and colleagues[5]. The coherent array of models in TA explains structure and function of personality, how and why people communicate and develop relationships in particular patterns, how and why they develop certain attitudes towards self and others and how these can be changed. Apart from its use in psychotherapy and counselling, it is being applied in the field of education and organizations[5]. The beauty of TA is the combination of its simplicity and profoundness. The logical appeal and systematic approach of TA would make it palatable to medical doctors. TA models can be used to gain insights and solve the problems in DPR. Objective of this article is to describe the historical and present scenario of DPR and its future with appropriate TA models.

Editor's Comment :

- Transactional Analysis (TA) is a social psychology theory and practice appropriate to improve dynamics of Doctor Patient Relationship (DPR). TA shows prevailing conflicts analysed as 'games' occur due to the failure of traditional 'symbiotic' model of DPR. Contractual relationship is a harmonious model of DPR appropriate for modern era.

Ego state model of personality :

Ego state model of personality is a core concept in TA. Eric Berne defined an ego-state as a consistent pattern of feeling and experience directly related to a corresponding consistent pattern of behaviors[6]. There are three ego states in any person – Parent, Adult and Child. If a person thinks, feels and behaves like one of his or her parent or parent-figures such as teachers, he or she is in Parent ego state. If person thinks, feels and behaves as he or she used to do in childhood, he or she is in Child ego state. If one person's thoughts, feelings and behaviour are appropriate for here and now situation and considers all options available for responding, that person is in Adult ego state (Fig 1a). Adult ego state use demands awareness of self, others and environment where as the other two ego states

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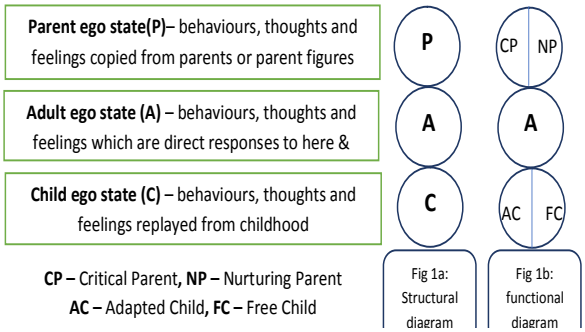

Figure 1: Ego state Model of Personality in Transactional Analysis (Modified from source)[7]

are automatic behaviours. The Parent function may be Controlling/Critical (CP) or Nurturing (NP). Child may function in a Free (uncensored) manner (FC) or in an Adapted manner (compliant or rebellious) (AC) (Fig 1b). These functions can be positive or negative depending on the contexts[7].

In consultation office, doctor is likely to be using Parent and Adult ego states and; patient is likely to use Child ego state to relate to each other. They may continue to interact from these ego states indefinitely or may shift to other ego states which would make the relationship uncomfortable. A systematic analysis of DPR is carried out with further models built upon the ego state model.

Symbiosis – Historical Paradigm of Doctor-patient Relationship :

Traditionally, Doctor-patient relationship had been symbiotic. The term symbiosis in TA by default refers to an unhealthy relationship. Typically, one individual excludes use of Parent and Adult and; other individual excludes use of Child in the relationship. There can be situations when symbiosis is appropriate as well, for example, a mother taking care of her infant (infant has not developed Parent and Adult ego states) or a doctor taking care of an unconscious or disoriented patient (both Parent and Adult ego sates of patient are physiologically decommissioned)[1].

In symbiosis, only doctor thinks through different treatment options (Adult) and judges what is good and bad for the patients (Parent) while the patient categorically abides (Child) by those decisions. If any uncomfortable or untoward outcome occurred, patient or family members would still look upon (Child) the doctor to console them. They interact as though there are only three ego states between them instead of six (Fig 2). Symbiosis was appropriate for the era of intuitive medical practice. Patients were not resourceful to contribute to the intuitive process. Doctors would not be able to involve patients in decision making even if

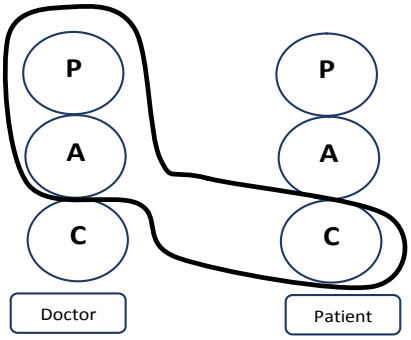

Figure 2: Symbiotic relationship between doctor and patient (modified from source)[7]

they wanted to because, there is no explanation for intuition.

Symbiosis is an outdated model of DPR in the era of Evidence-based Medicine. Though the relationship seems stable, there are potential dangers involved in it. Patient would get exploited and doctor would suffer burn out. The academic demands of the profession, family and social responsibilities of the doctor are different from that of olden times. In other words, doctors have to consider their own needs (Child). Modern diagnostics and treatment modalities are potentially thought provoking for patients and, educated individuals are capable to think and judge (Adult and Parent). Hence, symbiosis cannot be a stable model of DPR in modern era. However, both parties attempt at creating a symbiotic relationship due to historical relics and eventually fail in maintaining it.

Game – The Current Paradigm of Doctor Patient Relationship :

A unit of social discourse between two individuals is termed as transaction. Transactions actually occur between ego states of individuals[7]. In symbiosis, only two sets of transactions occur – one between Child of patient and Adult of doctor and the other between Child of patient and Parent of doctor. In the modern scenario, Child of doctor and; Adult and Parent of patient are also activated in the relationship.

If a transaction contains a covert message behind the overt message, it is called ulterior transaction[7]. This happens when more than two ego states interact together. The covert message is conveyed by non-verbal cues such as posture, gestures, tone and modulation of voice which are incongruent with the spoken words (overt message)[7]. However, covert message emanates without awareness. For example, a family member frantically enquiring about the patient, “doctor, how is she?!” may also be conveying that “you must tell me she will be alright otherwise, I would breakdown right

now". The overt message is from Adult and the covert message is from Child (Fig 3). Doctor feels emotionally challenged and speaks "Her condition is serious but, we will do whatever is possible" may also convey that "she will be alright; I will cure her especially serious condition". The overt message is from Adult and the covert message is from Parent (Fig 3).

Berne defined game as series of ulterior transactions with a gimmick, leading to a usually well-concealed but well-defined pay-off[8]. Pay-off is the bad feeling generated at the end of the series of ulterior transactions which may have been continuing over a few minutes to years. The pay-off can be of different degrees ranging from a mild disconcertedness to physical violence depending on the temperaments of the involved individuals[7]. The high degree pay-offs make it to media news where as low degree pay-offs would only be topics for trivial chit-chats.

As a continuation of the example discussed earlier, when an unfortunate outcome occurs though it was expected and explained, the family member will cry foul, "you said she will be alright! What wrong you have done?!" and the doctor would reply "I never said she will be alright! Is this the recognition you give me for all my efforts?!". A shift in ego states of both parties has happened at the close of the game – the family member shifted from Child to Parent while doctor shifted from Parent to Child. The game here was a failed attempt at symbiosis. Expectation of doctors from patients to be 'ever grateful and compliant' and the fantasy expectation of patients that doctor must be 'next to god' are complementary.

Given the probabilistic nature of course of diseases and unknown temperaments of the individuals, degree of pay-off of the games played in healthcare settings are unpredictable. Hence, games are to be addressed in toto whereas, the public discourse is about addressing only high degree pay off, the violence.

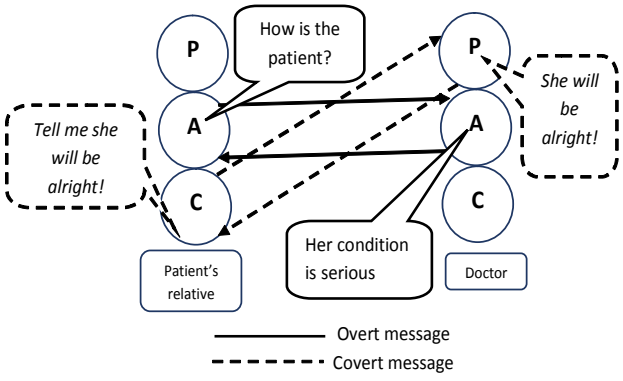

Figure 3: Example of an ulterior transaction in game relationship (Modified from source)[7]

Games need to be replaced by contracts which is a potentially stable model of DPR appropriate for modern era[7].

Contract – the future paradigm of doctor patient relationship :

In TA, the word contract refers to a typical relationship dynamic. James & Jongeward defined contract as Adult commitment to one's self and/or someone else to make a change[9]. The contractual relationship is established between Adult ego states of two individuals (Fig 4). The doctor shall take up the responsibility to direct the patient and family to use their Adult ego state. Transactions must be carried out with Adult awareness. Given the probabilistic nature of disease course, there must be clarity for the patient and family about the probabilistic ramifications of medical treatment from early on about the time and resources involved. Expectations and responsibilities must be negotiated mutually[7]. In the initial contracting, need for re-contracting with eventualities also must be agreed upon. Claude Steiner specified four requirements for an effective contract – mutual consent, appropriate recompense for the professional for the time and effort, competency of the doctor and the competency of the patient to carry out the agreed course of action and lawful goal and course of action[10]. In legal settings, the word contract refers to explicit written statements on agreements. In contractual relationship, the explicit nature and openness are hallmark of every transactions including the written documents.

Though the concept of contract is straightforward, in practice, the unaware psychodynamics would ruin it degrading to games. Adult ego state has the ability to evaluate thoughts and feelings in Parent and Child ego states and can choose to use any of them to behave if appropriate in the given context (Fig 4). The doctor must be watchful for covert messages from self and patient and must address it overtly[7]. In the previous example, when the family member enquires frantically,

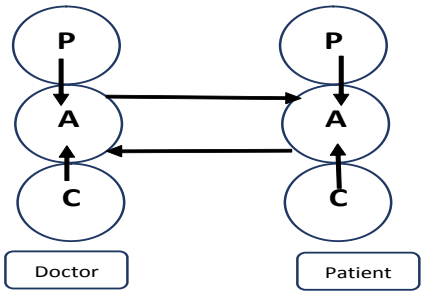

Figure 4: Transactions in Contractual relationship (Modified from source)[7]

the doctor will have to the make the covert message overt respectfully, "I see that you are emotionally overwhelmed. I am afraid, you are at the verge of breakdown". Then, stimulate the person to use Adult ego state with questions such as "what do you understand about her present condition?". These kinds of conversations are structured in communication models such as SPIKES protocol for breaking bad news[11].

It is obvious that to establish a contractual relationship, more time is required and systems need to be reoriented. Often, the contracts are multi-party. For example, a patient visiting a doctor at a hospital is in a minimum three-party contract – involving hospital administrator, doctor and the patient. The problems arise out of the vague nature of expectations and responsibilities of the parties to each other. National Accreditation Board for Hospitals & Health Providers stipulates display of patients' rights and responsibilities at their premises[12]. Such measures stimulate the parties involved to use their Adult ego state. Many such system changes in a coherent manner are required to establish and maintain a contractual Doctor-patient Relationship. Doctors who are convinced that symbiosis is out dated model, would advocate for contractual relationship from all concerned parties. Transactional Analysis gives array of tools to bring about changes in organizations actively and systematically.

Conclusion

Symbiosis was a stable model of DPR relevant in the olden times. Current conflicts in healthcare settings are due to game relationships which are failed attempts at establishing symbiosis. Contractual relationship is a stable model of DPR appropriate for modern era. TA can be one of the systems to analyse and address the current challenges in Doctor-patient Relationship.

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Review Article

Evolution of Biomarkers for Frailty over the Last Decade : A Literature Review

Anisha Galhotra[1], Monica Gupta[2], Sarabmeet Singh Lehl[3], Arnav Galhotra[4], Dhriti Sood[1], Ankit Gauba[1]

Aging is a Complex Physiological Process which involves remodeling of cellular components and processes, decline of functional reserve, adaptation of the body to these changes and finally senescence. An important concept in ageing physiology is Frailty which is a physiological, age-related condition characterized by a decrease in functional reserve across multiple organ systems. The phenotype of physical frailty has five components, that is, slowness, weakness, low physical activity level, unintentional weight loss and exhaustion It is crucial to mention "Inflammaging", a term that signifies the development of an age-related inflammation in the body wherein there is an increase in acute phase reactants and pro-inflammatory cytokines contributing independently to the pathogenesis of frailty. Inflammaging has been proposed to be associated with frailty and many studies suggest the existence of a relationship between age-related Frailty and inflammatory Biomarkers. The aim of this review is to study the evolution of our understanding of the role of inflammatory markers in development of Frailty in the older population.

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Key words **: Frailty, Biomarkers, Inflammation, Aging.**

Frailty has been accurately defined by the International Association of Gerontology and Geriatrics (IAGG) Frailty Consensus as a reduced strength and physiologic malfunctioning that increases an individual's susceptibility to increased dependency, vulnerability and death[1]. Frailty develops when there is multi-system decline or failure. The number of systems involved contribute to the impact of frailty[2]. The implication of a person being labeled frail is that the severity of illness is likely to be more and the chances of recovery less than in pre-frail or individuals without Frailty.

Our understanding of Frailty has drastically improved with time. Aging, illness, poverty, immune status, endocrine factors are all believed to cause and affect frailty in an individual[2]. Inflammation is one of the pathways and an established causative factor for Frailty. Thus, Frailty is multifactorial and a single pathophysiological process cannot be ascribed to the genesis of Frailty. It is a result of cumulative cellular damage gathered over time with factors an interactive role[3]. In a robust individual, there are homeostatic buffers which prevent decline of function even after any insult to the body and retard progression towards debility. It is only when a limit is surpassed that frailty develops in an individual. This threshold is strongly determined by the age of an individual and decreases as one ages, because the homeostatic reserve of the body tends to with time[4].

Editor's Comment :

- Functional decline rather than the chronological age of the individual is more consistent with the concept of aging.
- Inflammaging plays a pivotal role in induction and progression of frailty in elderly.
- Frailty incident to increasing age is associated with higher levels of inflammatory markers.
- Early detection of frailty by use of biomarkers may prove useful in reversing the condition.

Frailty is thought to be reversible, so early detection may prove useful in returning the subject to state. Frailty can be measured using different scales. In 2001, Fried and colleagues designed a scale which used clinical parameters to assess and grade frailty. The five physical features of the Fried, *et al* criterion are: unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity[5]. Individuals can be categorized into being in one of the 3 states; robust or non frail, frail and dependent. The stages of Frailty, based on the Fried phenotype criterion are; A person is not frail if the score is 0; 1 or 2 score implies increased risk of becoming frail and are hence termed as pre-frail; A score of 3-5 suggests frailty. This was

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followed by another breakthrough when Rockwood and Mitnitski proposed another Frailty criterion which includes Psychosocial aspect of Frailty along with the physical aspect[6]. Both these scales are, today, the most commonly used scales for the measurement of frailty.

The current review includes studies which used either of these criteria for measuring frailty. Pro-inflammatory cytokines promote protein degradation and affect important metabolic pathways and thereby influence Frailty[7]. The review focuses on the evolution of using inflammation as the key risk factor for induction and progression.

Materials and Methods

Search strategy :

Studies were sought through an extensive bibliographic search making use of these databases: PubMed, Embase, CINAHL, Medline updated to January, 2021. The search terms used were (frailty) AND (inflammatory biomarkers) OR (cytokines) AND (elderly).

Eligibility criteria for selection of studies :

The studies included in this systematic review are cross-sectional, cohort, prospective studies or randomized clinical trials. Only the trials conducted on populations aged more than 65 years were selected. Frailty criterion used in studies was Fried Frailty phenotype criterion[5]. Another criterion used was Rockwood Frailty Index[6]. When we found papers published by the same author/s, we included only the complete ones and the most recent ones in the study. Only the trials and studies conducted on humans were included in the review. Important outcomes pertaining to the title of the review, that is, any significant rise in inflammatory markers, general inflammatory profile, levels of endocrine immune markers, racial and gender variations and topography were evaluated and relevant findings were taken into account. Only the studies and trials in English were considered. Studies having confounding factors such as other comorbidities were excluded. We tried to identify publications describing the relation of inflammatory Biomarkers as an index of Frailty in the elderly. 11 were selected for the systematic review out of the 53 relevant articles found.

Study characteristics :

The studies done were from multiple Countries in different Continents and thus provided a universal view-point. The studies were during different time periods and therefore, the evolution of our understanding of the concept of Frailty and its association with inflammation. We have summarized the relevant details of each study in a tabulated form (Table 1).

Data collection :

The information that was extracted from various studies included: Author, Year of publication, Country, Type of study, Sample size, Frailty criteria, Inflammatory biomarkers and Conclusion. The studies are presented in Table 1 along with their findings.

Discussion

This review shows that from 2013 to 2020, numerous markers were linked frailty. Conclusions of the studies varied across the studies, but it was uniformly observed that a multitude of inflammatory markers were associated with increased incidence of Frailty among elderly. In the beginning of the decade, a prospective study by Gale *et al* indicated that C-reactive protein and Fibrinogen levels were significantly associated with Frailty and this association was more pronounced in women[8]. Endocrine markers also emerged as causal factors for frailty. Baylis *et al* concluded that levels of White cell count, neutrophils, monocytes, ESR and dehydroepiandrosterone augmented the frailty status of an individual[18]. The study by Lai *et al* focussed on institutionalized men which were an unexplored subset of the elderly population at that time[10]. Their contribution revealed a strong correlation between IL-6 and incident Frailty in the population of older men above 65 years of age. However, contrary to the previous studies, no significant association was observed with CRP or TNF-alpha. The plausible explanation lied in the exclusion of persons with co-morbidities in this study; as authors argued that co-morbidities might have led to increased CRP and also Frailty in previous studies[10].

The year 2016 marked the beginning of a change in how we looked at “Frailty and Inflammation”. Lu *et al*, through their cohort of 76 participants found a direct association of Frailty with soluble glycoprotein 130 (sgp130) and IL-6 receptors[12]. As the levels of these markers are more stable these are considered more reliable indicators of Frailty. This study is consistent with the notion that changes in cytokine migration and chemokine response alter Frailty in elderly[12].

One of the significant findings in the year 2017 was a weak association of frailty with IL-8 levels, seen in the study done by Hsu *et al*[13]. Later in 2017, study by Langmann, *et al* on long-term-care female residents threw light on levels of inflammatory markers at 12 and 24 months following start of the trial and any subsequent development or progression of Frailty[14]. Their study shows functional decline with time in

Table 1 — *Studies showing association of frailty with inflammatory markers*

Authors	Year of publication/ Country	Type of study/ Sample size(n)	Frailty criteria	Inflammatory biomarkers associated
Gale CR *et al*[8]	2013/ U.K.	Prospective study/ 2146	Fried frailty phenotype criteria	For each SD unit increase in CRP and fibrinogen levels, an odds ratio greater than 1 was observed. implies the association is positive and significant.
Baylis D *et al*[9]	2013/ U.K.	Cohort study/ 254	Fried frailty phenotype criteria	A plethora of inflammatory markers consisting of WCC, T4, ESR, lymphocytes, neutrophils, monocytes and DHEAS was shown to be associated with increased risk of frailty.
Lai HY *et al*[10]	2014/ Taiwan	Prospective study / 386	Fried frailty phenotype criteria	Trends towards a high IL-6 with frail status was demonstrated. Association of TNF- alpha was seen both in adjusted and unadjusted for age trails.
Zhu Y *et al*[11]	2016/ China	Cross – sectional study/1478	Modified frailty phenotype criteria	Approximately a quarter of participants were categorized into high CRP group, one-eighth in low CRP and more than half in intermediate CRP group. From high to low CRP, hospital admissions increased linearly.
Lu Y *et al*[12]	2016/ Singapore	Cohort study/ 76	Rockwood frailty index and Fried frailty phenotype criteria	Positive associations of the Frailty Index with levels of soluble glycoprotein 130, I-309, B-cell attracting chemokine 1, RANTES, and leptin were observed. MCP-1 showed an inverse relation with the Frailty Index.
Hsu B *et al*[13]	2017/ Australia	Cross sectional study / 1705	Fried frailty phenotype, Rockwood frailty phenotype criteria	For each SD increase in levels of IL-6, men were at more risk of developing frailty when compared to robust individuals. For each SD increase in IL-8, males have an odds ratio of 1.16 more likely to be pre- frail and 1.28 for being frail. IL-8 continued to be associated with frailty when adjusted for age.
Langman GA *et al*[14]	2017/ U.S.A	Double blind RCT / 178	Modified Fried frailty index	Frail participants had higher levels of CRP, TNF- alpha- R1, TNF-alpha R2, IL-6, IL-6-R.
Marcos Perez D *et al*[7]	2018/ Spain	Cross sectional study/ 259	Fried frailty phenotype criteria	Levels of TNF-R2, TNF-alpha, IL-6 and CRP were seen to be high in frail participants.CD19+ cell concentration significantly decreased in the frail group.
Semmarath W *et al*[15]	2019/ Thailand	Cross sectional study / 526	Fried frailty phenotype criteria	Both inflammatory markers (CRP and IL-6) were increased in the frail group of patients, irrespective of the sex of the patient. IL-6 was reported to be more associated with frailty risk.
Marzetti E *et al*[16]	2019/ Italy	Cross sectional, case control/1200	SPPB	Physical frailty and sarcopeniacytokinome includes higher levels of CRP and lower concentration of MPO, IL-8, MCP -1, IF alpha, FGF-beta, TNF -alpha, MIP-1 beta, IL-17.
Palmer J *et al*[17]	2019/ U.S.A	Prospective analysis/100	Trauma specific frailty index	Frailty associated pro-inflammatory biomarkers observed were IL-1beta, IL-6 -2 alpha, TNF- alpha and endocrine biomarkers IGF-1 and GH.

SD: Standard deviation; CRP: C-reactive protein; WCC: White cell count; ESR: Erythrocyte sedimentation rate; DHEAS: Dehydroepiandrosterone; IL-6: Interleukin-6; TNF-alpha: Tumor necrosis factor- alpha; RANTES: Regulated upon activation normal T cell expressed and secreted; MCP-1: Monocytes chemoattractant protein 1; RCT: Randomized clinical trial; CD: Cluster of differentiation; SPPB: Short Physical Performance Battery-score; MPO: Myeloperoxidase; FGF-beta: Fibroblast growth factor-beta; MIP-1:Macrophage inflammatory protein; IGF-1: Insulin like growth factor-1; GH: Growth hormone

subjects having higher baseline levels of IL-6, CRP and TNF-alpha irrespective of baseline comorbidities.14 In the study by Marcos Perez D, *et al* explored immune markers in elderly and a slight decrease in CD19+ cells was observed in the frail group. An increase in the CD4+/CD8+ ratio in frail subjects was also significantly prominent[7]. The study also suggested that sTNF-RII levels may have clinical relevance in screening for Frailty since TNF-alpha gets shed and cleaved into sTNF-RI and sTNF-RII which can be measured more accurately in blood to look for significant TNF-alpha activities[7]. Marzetti *et al* found an inverse relationship between Frailty and levels of myeloperoxidase, platelet derived growth factor BB isoform (PDGF-BB), IL-8 and monocytes chemoattractant protein 1.16. Their study pivoted around the cytokinome in frail patients and hence entails the discussion regarding muscle atrophy and degeneration in a frail individual. Interferon gamma induced protein 10(IP-10) is implicated as a marker of muscle atrophy and hence leading to physical Frailty and Sarcopenia according to their study. P-selectin levels the walking speed and high levels were found in older frail women[16]. The studies support an association between age-related chronic inflammation and development of Frailty. These findings can be put into use for early identification of frailty by using certain Biomarkers as diagnostic tools and preventing progression of Frailty into severe functional disability. The individual contribution of the various Biomarkers is discussed at length below.

CRP and Frailty :

C-reactive Protein (CRP) is an inflammatory Biomarker whose production is upregulated in inflammatory and infectious conditions by the Liver and becomes detectable in the blood after 6 hours and peaks within 36-48 hours[19]. With increasing age, a chronic, low grade inflammation sets in, also termed as inflammaging, leading to decrease response to antigens. Studies by Kenny RA *et al* in the 1980s, first, described elevation of CRP in acute infections in the elderly population[20]. CRP can also be used as a major prognostic marker in most of the pathological states. CRP levels are directly proportional to the intensity of inflammation and, thus, higher CRP levels indicate a more severe disease and prognosis. CRP concentration increases during aging and may contribute to the pathogenesis of age-related Cardiovascular events and Diabetes[21]. It was seen that this association was far greater in women than in men. One potential explanation is that women have more adipose tissue which results in increased CRP production by the Hepatocytes in women. This also suggests that obesity triggers inflammation and has more influence Frailty in women[8]. Raised CRP levels ve detrimental effects on multiple organ-systems Sarcopenia, Anaemia, Glucose intolerance and Blood dyscrasias. All of this ultimately culminates into adverse health outcomes including falls, disabilities, dependencies and death.

IL-6 and Frailty :

Interleukin-6 is an inflammatory marker produced by many different cells. Levels of IL-6 increase with age and are also associated with many of the age related diseases. Increased IL-6 concentrations have been shown to be associated with increased risk of developing disability and reduced muscle strength[10]. Grip strength is also a component of Frailty criterion which is more specifically associated with increased levels of inflammatory cytokine, IL-6. This is consistent with the other studies where increased levels of IL-6 were found to lead to Frailty because they caused decrease in muscle mass and muscle strength that resulted in reduced grip strength; a specific weakness phenotype[22]. Some studies also found that IL-6 through its inhibiting effect on Erythropoietin also caused anemia. Cellular senescence is a major causal factor of Frailty which develops with increasing age. Senescence inducers cause mutations, DNA damage, reactive metabolites and proteotoxic stress which, by activating tumor suppressor genes, initiates the senescence response. Chronic inflammation and tissue dysfunction are the result of the infiltration and phenotypic changes of immune cells by the senescent cells[13].

TNF- alpha and Frailty :

TNF-alpha is a cytokine produced by macrophages and monocytes. It upregulates the production of IL-6 and mediates immune mechanisms both in normal as well as pathological states. Increased levels of TNF-alpha in frail patients have shown to increase the rate of skeletal muscle cells apoptosis. Serum levels of TNF-alpha were reported to be directly proportional to IL6 and CRP levels in geriatric population that suggests activation of the entire inflammatory cascade. Some studies also showed lower levels of TNF-alpha. One reason for the above statement could be that TNF-alpha induces IL-6 production but appear in circulation. Moreover, being a less stable marker; TNF-alpha is a relatively less reliable indicator of chronic inflammation[10].

Fibrinogen and Frailty :

Fibrinogen, a glycoprotein, consists of 6 subunits: two alpha, beta and gamma respectively. It is

synthesized in the Liver and is involved in the coagulation cascade. Levels of Fibrinogen have been found to influence the Frailty status of an individual[23]. Conversely, physiological changes subsequent to aging also affect the coagulation profile through their actions on fibrinogen[8]. Higher baseline concentration of fibrinogen was found to be associated with higher incidence of frailty among women[23]. The effect accentuated when the baseline concentration of CRP was also higher[23].

IL-8 and Frailty :

IL-8 is a Cytokine produced by Phagocytes and Mesenchymal cells under inflammatory stimulus and activates Neutrophils producing a plethora of effects. Activated Neutrophils undergo chemotaxis, exocytosis and respiratory burst. IL-8 is one of the meditators responsible for Neutrophil migration and accumulation at the site of inflammation[8]. IL-8 was found to be weakly associated with Frailty. For one SD increase in IL-8, there was increased odds-ratio for developing frailty in men. IL-8 showed positive association with frailty even when adjusted for age.

Other markers and Frailty :

Baseline levels of other markers; Neutrophils, WCC, Monocytes, Lymphocytes, ESR, freeT4, DHEAS, ratio of cortisol to DHEAS is found to be relevant in predicting Frailty as these markers, directly or indirectly, lead to development of the state of inflammaging[13]. The concept of inflammaging states that aging is associated with an increase in the inflammatory Cytokines and hence the Leukocytes and acute phase reactants.

Clinical relevance :

With the help of this literature review, we have reviewed the relationship increasing age marked increase in the levels of the inflammatory markers. Most of the evidence suggests that the levels of CRP, IL-6 and to some extent, TNF-alpha are consistent with the concept of inflammaging and that these markers can be used to assess the Frailty status of individuals, especially the elderly[24]. Measurement of Serum CRP levels is being considered as an appropriate screening test but its use is limited to the detection of pathological or various inflammatory states. These studies support the use of CRP and IL-6 as diagnostic tools for frailty in elderly which could help predict the susceptibility of an individual to disease and disability. To study the role of immune markers in the oldest old, more studies are required. There are some studies that provide contradictory evidence to the findings of the above studies and there are some that incriminate other inflammatory markers in Frailty. We still need confirmatory evidence so as to use these markers in real world settings to diagnose and delay or reverse Frailty wherever feasible. This is clinically very relevant as population over 60 years is expected to be more than 22% of the world population by 2050 and the clinician is bound to see significant multi-morbidity in the years to come[25].

Conclusion

Frailty incident to increasing age is associated with higher levels of inflammatory markers. After reviewing the pertinent literature, CRP and IL-6 can be strongly associated with the development of Frailty in the elderly. The elevated levels of CRP and IL-6 were consistent both in community and hospital settings and across geographical regions. However, the effects of other immune markers cannot be ignored. TNF-alpha and IL-8 have also shown to be associated with increased Frailty, besides Fibrinogen. Majority of the studies showed a generalized increase in the inflammatory Biomarkers favoring the concept of inflammaging.

In conclusion, the pathogenesis of Frailty is poorly understood; however, this review examines the evolutionary concepts and current evidence to a growing link between inflammation and Frailty. Chronic immune dysregulation or imbalance associated with inflammation is a better putative justification for the biologic basis of Frailty and functional decline rather than the chronological age of the individual. How this inflammaging can be reversed by modulating the inflammatory cytokine milieu is a matter of further research.

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Review Article

Hydatid Disease — An Overview

Ananda Bagchi[1], Aradhya Sekhar Bagchi[2]

Human Hydatid Disease is a growing menace, a parasitic disease present in many countries all over the globe (more than 1 million people are affected throughout the World annually). Tape-worm is the main causative organism.In humans it is prevalent in two forms – Cystic Echinococcosis (CE) [caused by Echinococcus granulosus] and Alveolar Echinococcosis (AE)[caused by Echinococcus multilocularis]. Humans are the accidental intermediate host; they are being affected by drinking water or eating food contaminated with parasite eggs or by direct contact with infected animal hosts like dogs. In humans, the most commonly affected organ is Liver followed by the Lungs. The main investigational tool is Ultrasonography but Computed Tomography (CT) and serological tests are also helpful in the diagnosis of Liver Hydatid Cysts (LHC).

Although PAIR technique is the most important modality of therapy along with medical treatment, surgery has got a great role in the management of the entire spectrum of the disease. Nowadays, various Laparoscopic techniques have been safely used to improve the morbidity and mortality associated with the surgical management of the disease, and is the only other therapeutic option used all over the World.

Prevention programme includes, public awareness and Education, dog deworming and slaughterhouse hygiene.

[*J Indian Med Assoc* 2022; **120(8):** 65-70]

Key words **: Hydatid, Echinococcus, Dog tapeworm, PAIR, Albendazole.**

Hydatid disease is a gradually progressive parasitic disease caused by a tape-worm having 2 species- Echinococcus granulosus and Echinococcus multilocularis. The number of cases has been gradually increasing for last couple of decades, especially in the sheep rearing areas of USA and also in the Indian subcontinent[1] due to intercontinental migration of people. So now, physicians have to be more aware and careful about the clinical profile of hydatid disease and its management strategies.

About the Parasite :

There are four known species of echinococcus[1], out of which three species affect humans. They are –

1. E Granulosus causing cystic Echinococcosis (CE), also known as Hydatid disease or Hydatidosis and is the most common amongst all the members. cDNA encoding calmodulin[3], a calcium sensor protein (r Egcam)[2] which has got a direct role in the life cycle of E. granulosus.

2. E Multilocularis- It causes alveolar echinococcosis. Most virulent but rare.

3. Other two forms of Echinococcosis:

a) Polycystic- caused by **E vogeli**

b) Uncystic – caused by **E Oligoarthrus** are also detected.

Hydatid disease, with it's twin phenotypes of cystic and alveolar echinococcosis, is therefore a major public health as well as medical problem.

Editor's Comment :

- Hydatid disease is a parasitic disease which is showing increasing incidence all over the world. It is therefore prudent to have a thorough grasp of the pathophysiology, the life cycle of the parasite, the imaging and classification systems, as well as the various management options available. It is also important for physicians to know about alveolar echinococcosis which can be a great mimicker of various other disseminated infectious/malignant diseases.

Mode of Transmission :

Larval cestodes of the phylum Platyhelminthes (tape worms) cause Echinococcosis.

Their life cycle involves two hosts –

1. One Definitive Host– Dogs and other carnivores act as a definitive host.[4] They become infected by consuming the viscera of intermediate hosts,thereby harbouring the mature tapeworm in their intestine.

2. One Intermediate Host– Few herbivorous and Omnivorous animals which act as intermediate hosts, gets the infection by ingesting parasite eggs found in contaminated food and water and parasite grows into larval stages in their viscera.

The life cycle has three developmental stages –

a) The adult tape-worm in the definitive host,
b) Eggs in the environment
c) The metacestode in the intermediate host.

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LIFE CYCLE — After ingestion by the definitive host, the metacestode matures into an Adult Tape-worm in the intestine of definitive host like dogs, which release eggs in their stool which are taken up by the intermediate hosts, sometimes accidentally, who subsequently hatch eggs, which ultimately infest the Liver, Lungs, Muscles and other organs of the intermediate host. The metacestodes are ingested by the definitive host.

Humans act as an accidental intermediate hosts[4], in the sense that they acquire infection in the same way as other intermediate host but are not involved in transmitting the infection to the definitive host.

Several distinct genotype of E Granulosus, are recognised, some having distinct host preferences. Some Genotypes are considered species distinct from E Granulosus. Not all genotypes cause infections in humans.In humans, the majority of cystic echinococcosis infection is maintained by dog – sheep –dog cycle.

Alveolar Echinococcosis (E multilocularis) usually occurs in a wild life cycle between foxes and other carnivores with small mammals (mostly rodents) acting as intermediate hosts. Domestic dogs and cats can also as definitive hosts.

E Vogeli is a rare species found in the bush dogs. It can easily infect other mammals that are exposed to its faeces.

Epidemiology :

Cystic Echinococcosis (CE) is found all over the World except Antarctica. It is mostly found in Mediterranean countries, the Middle East,South America (Southern part), Australia, New Zealand and parts of Africa(mainly southern); Central Asia[5,6] particularly China is also endemic for this disease. It is uncommon in Northern Europe.

The incidence of Cystic Echinococcosis (CE) in endemic areas varies from 1-220 cases per 100000 population while the incidence of AE ranges from 0.03-1.2 cases per 100000 population[6]. Infestation with E Vogeli is quite a rare form of Echinococcosis and is reported mainly in the Southern Parts of South America.

Age, Sex and Racial Distribution :

There is no sexual predilection for Human Hydatid disease.

Though the parasite affects all races equally, it has been seen that persons belonging to certain races in a specific geographical area are more affected; young adults in the age group between 30 to 40 years are mainly affected by CE whereas older debilitated age group(above 50 years) is mainly affected by AE.

Economic Burden due to Disease :

All over the Globe, more than 1 million people are suffering from CE and AE of which many people are suffering severe clinical symptoms which are sometimes life threatening, affecting their quality of life.

For CE, postoperative death rate is about 2.2% and relapse rate after treatment is about 6.5%.

Annually, around US $ 3 billion is being spent to cover losses incurred by the livestock industry.

Presentation of Human Hydatid Disease :

Human infection with E Granulosus most commonly affects the Liver (50% to 93%) and Lungs (25%); relatively uncommon sites are in the Bones (3%), Kidneys (2%), Spleen (1%), Muscles (5%), CNS (1%) or Eyes (1%). Cardiac hydatid cyst is a very rare presentation[7].

If Liver Hydatid Cysts (LHC) are not treated properly, they may have the following fates –

a) May develop fistulae with surrounding organs , intra/extrahepatic biliary apparatus.

b) Rupture into the peritoneal cavity with seeding of daughter cysts

c) Develop Daughter cysts inside itself or rarely die[8].

The disease can remain undetected for several years until Hydatid Cysts grow to an extent that gives rise to pressure effects especially in the brain or eyes.

Abdominal pain and pressure effects are initially vague; fullness, low grade fever, flatulence, nausea and vomiting are the cardinal symptoms of Liver Hydatid cyst. Sometimes pain in the epigastrium or right hypochondrium is also a presenting feature.

In Liver Hydatid Cyst, the cyst can produce Obstructive Jaundice symptoms by pressure effect, which can often lead to a misdiagnosis of metastatic deposits. With biliary rupture, the classic triad of biliary Colic, Jaundice and Urticaria is often observed. Bits and pieces of Hydatid membranes may be passed during emesis (hydatid emesia) and in the stool (Hydatid Enterica), rarely.

If the lung is affected, symptoms include chronic cough with expectoration (sometimes cyst membranes may be found with sputum), chest pain and shortness of breath. Other constitutional symptoms like malaise, weight loss, weakness, mild fever or pain in the extremities may also be present.

Alveolar Echinococcosis may be asymptomatic, with incubation period of 5-15 years. It develops slowly usually in the Liver, like a primary tumor, and therefore often mimics Cirrhosis of Liver or Hepatic Carcinoma, and may ultimately lead to hepatocellular failure.

When the parasite is disseminated in the bloodstream or via the lymphatic system, it may affect the Lungs, Brain or spleen, Causing specific symptoms; if left untreated, it is definitely fatal.

Diagnostic Approach :

Even though Human Hydatid disease may be asymptomatic for a long time or have non-specific symptoms, about 33% of the patients with Liver Hydatid Cyst (LHC) may present with pressure effects or complications.

The total diagnostic workup[9] includes.

(1) Routine Laboratory Haematological Examination which may Show – Leucocytosis (suggesting infection in the cyst), Eosinophilia is present in 25% of cases, there may be elevated bilirubin level along with raised Alkaline Phosphatase level, Hypogammaglobulinemia is present in 30% of cases.

(2) Casoni's Test – The test was first described by an Italian physicianTomaso Casoni in 1912.

It is a hypersensitivity based Intradermal Skin Test used to detect Hydatid Disease. Although once a major test in diagnosing Hydatid disease, it has largely been superseded by newer more sensitive, specific and safer serologic tests. Casoni's test is only 63.8% sensitive and 47% specific for diagnosing Hydatid disease.

(3) Serodiagnostic Techniques – Can be either antibody detection or antigen detection:

a) Antibody Detection : The indirect Haemagglutination test and Enzyme Linked Immunosorbent Assay (ELISA) have a sensitivity of 90% overall and are the initial screening tests of choice.

b) Antigen Detection : Double diffusion and Counter-immunoelectrophoresis methods were used, however they are not in vogue in these days.

Most Sensitive and Specific immunological test is IgG ELISA; and the sensitivity of ELISA for detection of Hepatic Cysts is more than that of Pulmonary cysts.

(4) Ultrasonography – USG is an indispensable tool in the diagnosis, treatment and follow up of Liver Hydatid Cysts. WHO informal working group on Echinococcus (IWGE)[10] classification of LHCs is presently accepted globally (Fig 1).

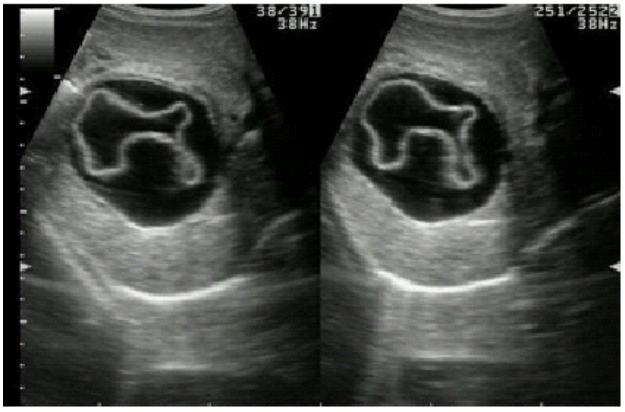

Fig 1 — Hepatic hydatid cyst - ultrasound water lily sign (Radiopedia)

Hepatic Hydatid Cyst - ultrasound water lily sign (Radiopedia)

USG Classification of Echinococcal cyst

CE1 – Active Unilocular Anechoic cyst with double line sign- Active Cyst

CE2 – Multiseptate Honeycomb cyst- Active cyst

CE3a – Cyst having Transitional biologic activity, showing detached membrane

CE3b – Cyst having Transitional biologic activity with presence of Daughter cysts in the solid matrix

CE4 – Heterogenous Hypoechoic / Hyperechoic cyst contents with no Daughter cysts- Inactive cyst

CE5 – Solid and calcified wall cysts- inactive cyst.

(5) Computed Tomography (CT scan) – CT scan is very accurate (98%) in diagnosing Hydatid Disease and its sensitivity in diagnosing Daughter cysts is very good in conditions[11] where USG fails as in obesity, excessive intestinal gas, abdominal wall deformities or previous surgical procedures (Fig 2).

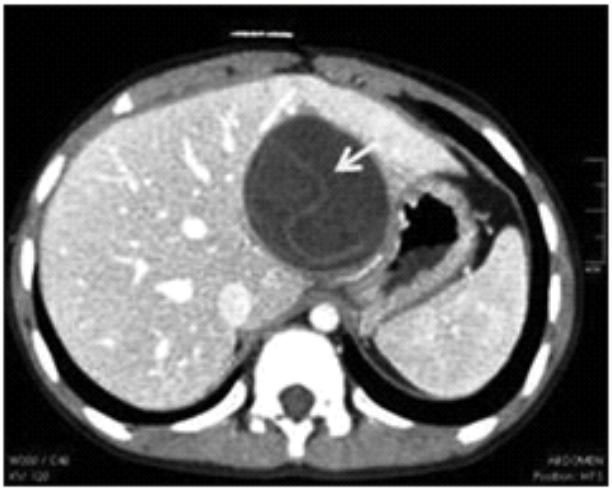

Fig 2 — CT Scan image (News-Medical.Net)

It is very effective in differentiating Hydatid Disease from amebic or pyogenic Liver abscess.Intravenous contrast is only used during CT scan when a communication with the biliary apparatus is suspected.

In AE, the CT Scan findings are sometimes indistinguishable from those of Hepatocellular Carcinoma.

In patients in whom an intrabiliary rupture is suspected, a perioperative ERCP is a good modality to establish cystobiliary communication, providing a therapeutic option at the same time.

(6) Magnetic Resonance Imaging (MRI)

MRI offers no real advantage over CT Scanning (Fig 3).

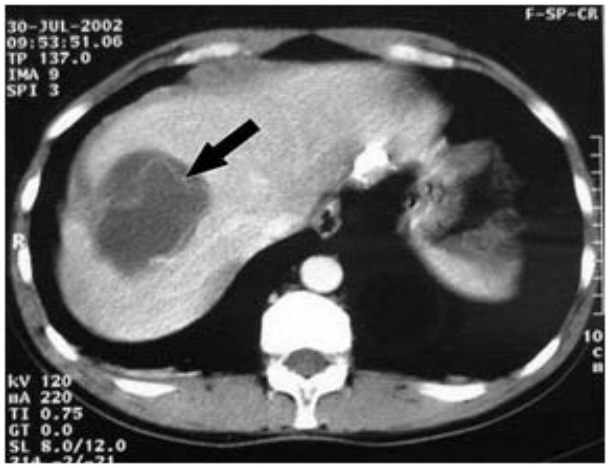

Fig 3 — The picture above is an image of the upper abdominal region, with a large cyst on the liver (arrow). Courtesy of Medline Plus

Different Diagnosis :

Many diseases simulate Hepatic Hydatid disease. They are –

a) Amoebic or Pyogenic Liver Abscess
b) Benign Hepatic Cysts (haemangioma)
c) Hepatocellular Carcinoma
d) Cysticercosis
e) Liver Metastasis
f) Budd Chiari Syndrome
g) Lung abscess in case of AE

Management Protocol :

There are various modalities for the treatment of Echinococcosis. They are –

1. Watch and wait
2. Percutaneous treatment (PT)
3. Medical treatment
4. Surgical treatment including Laparoscopic management.
5. Adjunctive treatment
6. Image oriented, stage specific treatment approach

(1) Watch and Wait :

As Hydatid Cyst is a slow growing disease, certain cyst types[12] are best left untreated and closely monitored over time. The consequences may be –

a) A large number of cysts eventually calcify without any treatment and without any symptoms.

b) Some cysts remain dormant, i.e. do not cause organ dysfunction or cause any symptoms for the patient; they need long term Ultrasonographic follow up for a period up to 10 years.

(2) Percutaneous Treatment (PT) :

Percutaneous treatment of LHC was introduced in 1980 and has become an attractive alternative to surgery and medical management[13].

The first PT that was used was PAIR[14] which includes USG or CT guided puncture of the cyst then aspiration of the cystic fluid, injection of a scolicidal agent (eg, hypertonic saline, 95% ethanol, albendazole or betadine) and then reaspirate the cystic content.

For unilocular cysts PAIR is a very safe and effective option. Great care is to be taken to avoid spillage and residual empty cavities are sterilised with 0.5% silver nitrate or 2.7% NaCl. PAIR therapy is contraindicated if cysts communicate with the biliary tract. PAIR includes a small risk of anaphylaxis in about 2% of cases but death due to anaphylaxis is very rare. Other percutaneous techniques are generally kept reserved for multivesiculated cysts or cysts with predominantly solid content which are very difficult to drain by PAIR method. Techniques are –

a) Percutaneous Evacuation (PEVAC);
b) Modified catheterisation technique (MoCAT);
c) Dilatable multifunction trocar (DMFT);
d) Radiofrequency thermal ablation (rarely used)

(3) Medical Treatment :

Drug therapy for Echinococcus is limited. The antihelminthic Benzimidazoles, namely Albendazole and mebendazole, are used for treatment and prophylaxis. Albendazole (10 -15 mg/kg/day orally) is used in the dose of 400mg twice daily orally for 3 to 6 months, in some cases it is used with alternating cycles of treatment and rest. Mebendazole (40-50 mg/kg/day orally) can also be used. Praziquantel, an isoquinoline derivative, is used in the dose of 20mg/kg twice daily for 14 days, as an adjunct for therapy.

Common side effects of the drugs are Alopecia and GI symptoms occurring in 1-5% of cases along with elevation of Liver enzymes. Benzimidazoles may suppress bone marrow functions may cause aplastic anaemia and also carry a risk to the foetus in the first trimester of pregnancy.

(4) Surgical Treatment

Previously, surgery was the only available therapeutic modality for LHC, for all different varieties of the disease[15].

Surgical techniques can be conservative or radical.

Among **Conservative Procedures,** Hydatidectomy and partial cyst removal are done, along with evacuation of the cyst contents; however there is considerable risk of anaphylactic shock and chemical Cholangitis. Also, the relapse rate is around 10-20%, with the residual cavity being the ideal seat for a secondary infection.

Radical Procedures target complete cyst removal sometimes along with a chunk of Liver tissue. Radical procedures exhibit a lower relapse rate but the intraoperative risk as well as the postoperative complications are significantly greater.

Laparoscopic surgical management of LHC[16] is gradually gaining ground nowadays. Various techniques like Total Pericystectomy, Puncture and aspiration of contents followed by Marsupialisation, Unroofing and Drainage, Unroofing and Omentoplasty and Omentoplasty using helical fasteners have been described. A major difficulty faced in Laparoscopic management of LHC is the difficultly inevacuating the contents of the cyst, the Daughter Cysts with the laminated membrane[17].

(5) Adjunctive Treatment :

There are evidences which showed that adjunctive measures play a useful role in the management. They are-

a) Prevention of secondary CE and relapses by Albendazole starting 4 days before surgery and continuing up to at least 1 month after surgery, but efficacy is doubtful.

b) Surgical field protection with pads soaked with scolicidal agents.

c) Prevention of Cholangitis – After surgery a search for cystobiliary fistula[18] is mandatory; if such a Phenomenon occurs, injection of scolicidal solution into the cyst cavity is contraindicated.

d) Cysts are always to be removed completely to avoid residual cavities. This prevents secondary infection or biliary fistulas and consequently achieves faster healing.

(6) Image Oriented Stage Specific Treatment Approach

WHO classification	Suggested modality of treatment
CE1	Albendazole alone if cyst <5cm, PAIR + Albendazole if >5cm
CE2	(Surgery + Albendazole) or (Non-PAIR PT + Albendazole)
CE3a	Albendazole alone if cyst<5cm: PAIR + Albendazole if >5cm
CE3b	(Surgery + Albendazole) or (Non-PAIR PT + Albendazole)
CE4 & CE5	Watch& wait

Complications :

Complications include –

(1) Related to parasite –
- a) Recurrence
- b) Infection
- c) Metastasis

(2) Related to medical treatment –
- a) Hepatotoxicity
- b) Anaemia & Thrombocytopenia
- c) Teratogenicity

(3) Related to PAIR intervention
- a) Spillage and seeding
- b) Haemorrhage
- c) Infection
- d) Mechanical damage to other tissue
- e) Anaphylactic shock
- f) Cystobiliary Fistula

(4) Related to scolicidal agents
- a) Chemical sclerosing cholangitis, especially if formalin is used.
- b) Hypernatremia, if hypertonic saline is used.
- c) Acidosis if cetrimide is used.

Prognosis :

In Cystic Echinococcosis,with good surgical evacuation of the cyst without spillage(which occurs in 2 to 25% of the cases) the prognosis is usually good. Operative mortality varies from 0.5% to 4% of the cases. The prognosis is guarded in case of alveolar echinococcosis, with cure being possible only with early diagnosis and complete surgical excision.

Prevention and Control of Hydatid Disease :

CE is a disease that may be easily prevented, with improved public awareness, improved slaughterhouse hygiene and periodic deworming of dogs with Praziquantel; These will ultimately impede disease transmission causing significant reduction in disease burden. A newer modality of prevention in the form of vaccinating sheep with an E. granulosus recombinant antigen (EG95) is nowadays being encouraged with good result.

Conclusion :

Human Hydatid Disease is a globally prevalent, slow growing disease having two phases- an evolving phase, wherein the cyst grows; and an involution phase, wherein the parasite dies, leaving a calcified cyst. Though treatment modalities are many, starting from medical treatment, PAIR and surgical treatment, complication often develop which may be sometimes life threatening. Now the focus is on preventive strategies which are to be adopted more and more to eliminate Cystic echinococcosis in humans in the near future.

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(Continued from page 78)

platelets in patients with active COVID-19 has revealed upregulation of many genes responsible for aggregation. Upstream regulators like JAK3 and Rho family GTPases were also activated in these platelets[3].

Compared to the other systemic manifestations of COVID, cardiovascular complications have received much less attention. A Cochrane review of cardiovascular effects of COVID revealed that the Weighted Mean Incidence (WMI) of AMI in hospitalized COVID patients was 1.7%[4]. In our cases, the diagnosis of AMI was established with the help of ECG, cardiac biomarkers and Echocardiography. Isolated elevation of cardiac biomarkers like Troponin T is found in a large number of COVID patients[4]. But in isolation, that does is not sufficient to diagnose AMI as such elevations can be transiently seen in hypoxia induced cardiac damage too. Thus, if the suspicion of AMI in a covid patient is high, a battery of tests should be advised instead of a single one like Troponin T. Both of our COVID-19 patients with AMI had fatal outcome.

Consultant Physician, Kolkata **Rudrajit Paul**

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Case Report

Spontaneous Nephrocutaneous Fistula in Xanthogranulomatous Pyelonephritis — A Rare Complication

Avinash P Dhok[1], Kajal R Mitra[2], Varun V Nimje[3], Shubham Bodhankar[4], Tushar Suresh Yadav[4]

The formation of fistulous tract between the kidney and adjacent organs is not uncommon while cutaneous fistulization is a rarer occurrence. We present a case of Nephrocutaneous Fistula without prior history of surgery or interventional procedure. Our case involves long standing obstructive pyonephrosis secondary to obstructing calculus at the ureteropelvic junction which led to formation of a fistulous tract upto the skin surface. This patient had complaints of purulent discharge from the right flank region associated with fever spikes since the last 1 month. The cutaneous manifestation in specific location should raise the possibility of underlying renal pathology.

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Key words **: Xanthogranulomatous Pyelonephritis.**

Fistula formation between the kidney and the skin is an uncommon condition, the common etiologies being secondary to surgery, interventional procedures, trauma[1]. Purulent contents tend to follow the pathway of least resistance, which is usually the bowel or some other adjacent organ[2]. However, formation of spontaneous Nephrocutaneous Fistula is a rare occurrence and only limited cases have been documented[3]. This text describes the features of spontaneous Nephrocutaneous Fistula secondary to longstanding obstructive renal calculus which resulted in Xanthogranulomatous Pyelonephritis.

Case Report

Our patient is a 52-year-old female patient who came with complaints of purulent discharge from right flank region since the last one month. Intermittent spikes of fever were present for which she took medications. There was no history of recent onset Pain, Tuberculosis, Diabetes Mellitus or Hypertension. No history of pulmonary or extrapulmonary tuberculosis was present among her family members. There was no previous surgical history or history of trauma.

On physical examination the patient was oriented and cooperative but had tenderness over the right flank with expulsion of serous, yellowish, foul-smelling discharge. There was fistulous opening present over the right flank region with discoloration of the surrounding skin and formation of nodules adjacent to the orifice due to granulation tissue. The discharge was initially haemorrhagic which later became purulent. Patient had taken different antibiotics for this discharge but the discharge was not relieved. Her vitals were within normal limits. Haematological investigations including serum creatinine were within normal limits with normal total Leucocyte Count and Haemoglobin. Urine microscopy showed 8-10 pus cells/HPF. There was no growth on the Urine culture.

Editor's Comment :

- Spontaneous Nephrocutaneous Fistula is a rare entity. In cases of such cutaneous manifestation in the lumbar region, underlying renal communication is to be kept in mind and the patient should be evaluated for the same.

On contrast enhanced CT examination, a large calculus was noted at the ureteropelvic junction resulting in dilatation of the renal pelvis and collecting system. Non enhancing collection was noted within the collecting system and renal pelvis which suggests infection. Non-obstructing renal calculi were also noted at the lower pole of right kidney. A linear tract was noted arising from the upper pole of right kidney and continuing upto the skin surface representing the fistulous tract. CT Urography Examination revealed non-functioning right kidney. This patient underwent a right sided radical Nephrectomy with excision of the fistula tract. On gross pathological examination of the surgically resected specimen, pus was present in the collecting system with chronic inflammatory changes detected in the Renal Parenchyma. On microscopic examination, Foamy Histiocytes, Multinucleated giant cells and Inflammatory cells were noted in the Renal Parenchyma suggesting diagnosis of Xanthogranulomatous pyelonephritis. There were no findings suggestive of Genitourinary Tuberculosis.

Discussion

Spontaneous fistulization from kidney to adjacent visceral organs is not unusual. However, spontaneous fistulization to the skin without previous Renal Surgery or

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intervention procedure is rare[4]. Nephrocutaneous Fistulae can develop from either Xanthogranulomatous Pyelonephritis or other chronic Renal Infective process. Penetrating or iatrogenic trauma can also be responsible for this. Patients usually present with local swelling and tenderness in the region of either flank. In rare instances, the fistula can develop which can extend down along the psoas muscle into the inguinal region or thigh resulting in formation of abscess. Pus discharge can be there and occasionally a calculus may be expelled at the external skin site through the fistulous pathway[5]. Rupture of pelvicalyceal system occurs whenever the elevated renal Pelvicalyceal System pressure secondary to an Obstructing Pathology causes extravasation of urine along the minimally resistant passage within the renal tissue. Maximum number of Pelvicalyceal System ruptures are because of calculi in the proximal ureter. Most cases of Nephrocutaneous Fistula are associated with non-functioning kidneys due to chronic obstruction.

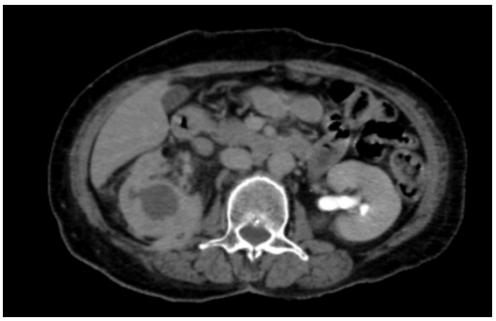

Fig 1 — Axial CECT image showing hypodense non enhancing collection within the right kidney with adjacent fat stranding

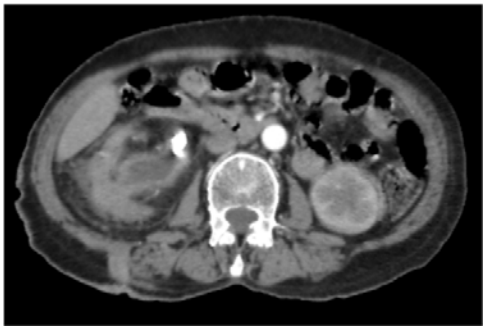

Fig 2 — A calculus seen at the right pelviureteric junction causing hydronephrosis in the right kidney

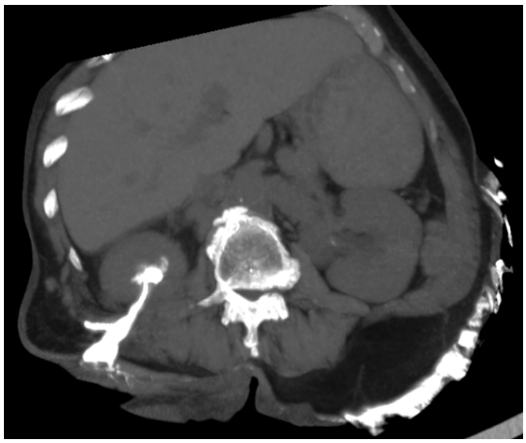

Fig 3 — Oblique axial maximum intensity projection image shows opacification of the nephrocutaneous fistula with positive contrast

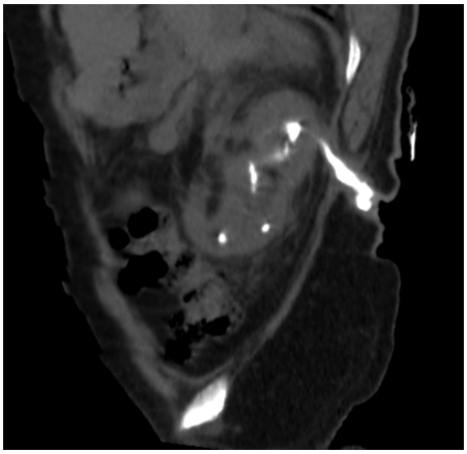

Fig 4 — Oblique sagittal maximum intensity projection image shows opacification of the nephrocutaneous fistula with positive contrast

The therapeutic approach for Nephrocutaneous Fistula is decided by the medical conditions of patient, presence of function in the Obstructed Kidney along with the reason for Nephrocutaneous Fistula[3]. Total Nephrectomy is advocated for Nephrocutaneous Fistula associated with staghorn calculus in a non-functioning kidney, although Heminephrectomy may be attempted in a duplicated kidney if only one segment is involved. Conservative treatment with specific antibiotic coverage for infection is an alternative in debilitated patients[6]. Excision of the tract of fistula is always performed in the similar operation, to reduce the chances recurrence and decrease patient morbidity[3]. Obstructing renal calculus responsible for the formation of Nephrocutaneous Fistula can remain asymptomatic for a long period of time and usually results in non-functioning kidney.

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Case Report

Amyand Hernia — An Uncommon Coexistence of Two Common Disease Entities

Rajib Datta[1], Shamita Chatterjee[2]

Amyand hernia is a very rare disorder characterized by presence of appendix (normal, inflamed or perforated) in the hernia sac. Though it is usually detected intra-operatively, ultrasonography or computerized tomographic scan done preoperatively may provide a clue. The presentation is determined by the condition of the appendix, and can mimic an incarcerated hernia. Though there are no standardized treatment protocols, management is mostly dictated by the condition of the appendix.

We present the case of a 62-year-old male patient who presented with right sided obstructed inguinal hernia, which intra-operatively revealed an Amyand Hernia.

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Key words **: Hernia, Appendix, Appendectomy, Amyand hernia, Inguinal hernia.**

Hernia, defined as the abnormal protrusion of an organ or part of an organ through the wall of the containing cavity, is one of the most frequent conditions that a surgeon encounters. Of all hernias, inguinal hernias are the commonest, with the omentum or bowel being the typical contents of the hernia sac. Appendicitis is another very common surgical condition. Very rarely when these two common entities co-exist, with the appendix (normal, inflamed or perforated) inside the hernia sac, it is called an Amyand Hernia (AH)[1].

We present the case of a 62-year-old male patient of AH.

Case Report

A 62-year-old male patient presented to the ER with right sided obstructed inguinal hernia. He was a chronic smoker with history of hypertension and COPD. Straight X ray abdomen showed multiple air fluids levels. Exploration of right inguinoscrotal region revealed a large indirect hernia with cecum, non-inflamed appendix and ileocaecal junction as contents. Appendectomy was not done as appendix was normal. Mesh was avoided (as the sac contained toxic fluid) and primary hernia repair was done, with posterior wall darning using 2-0 polypropylene. Patient had an uneventful recovery. Thus, it was an AH with normal appendix (Fig 1).

Discussion

In 1735, English surgeon Claudius Amyand first reported the presence of appendix in a hernia sac. This rare type of hernia was subsequently named after him**.**

Editor's Comment :
- **Very rare disorder.**
- **Usually diagnosed intra-operatively.**
- **Plan of management dictated by condition of appendix.**

AH accounts for between 0.19%-1.7% of all inguinal hernias[1]. It is three times more common in paediatric population, due to the patency of processus vaginalis[2]. In the paediatric population, the prevalence is 1% and occurs more often in males than females[2]. It typically presents on right side, possibly due to the normal

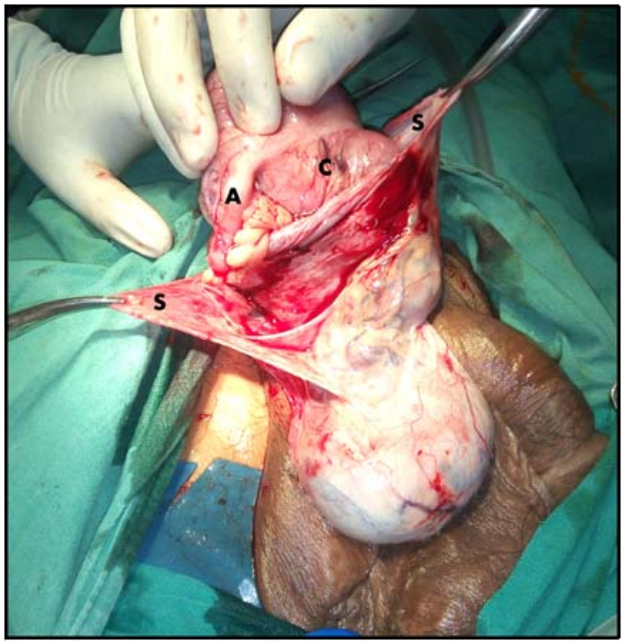

Fig 1 — Amyand Hernia with caecum (C) and appendix (A) as content in hernia sac (S)

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anatomical position of the appendix[3]. Although rare, left sided AH do occur and have been thought to be as a result of a mobile caecum,intestinal malrotation or situs inversus[4].

The pathophysiology of AH is uncertain. One theory suggests a congenital herniation of the appendix due to combination of an existing patent processus vaginalis and a fibrous connection between the appendix and testes[5]. Another theory points to the congenital laxity of the right colon since some of these cases contain the cecum in addition to the appendix[3].

The appendix may remain in the hernia sac without causing additional symptoms.But, though extremely rare, appendicitis may occurin 0.07-0.13% cases of AH[1]. When it does, it mimics an incarcerated hernia[5]. The appendicitis may either be due to primary inflammation causing oedema of the internal ring, or incarceration of a normal appendix by abdominal wall musculature[6]. Perforated appendix incarcerated within an inguinal hernia is rare as well, at 0.1% of all cases of appendicitis, with mortality ranging from 15%-30%, because of severe abdominal sepsis[1,5]. Other complications of AH may include abdominal or peri-appendicular abscess secondary to appendicular perforation[7], inflammation of right testicle and cord, testicular ischemia and rarely necrotizing fasciitis of the anterior abdominal wall[8].

Preoperative clinical diagnosis is usually impossible[1,5]. Though Ultrasound (USG) and Computerised Tomographic Scan (CT) may aid to a certain extent in identifying AH[9], these are seldom done for diagnosing a hernia. USG shows a blind ended tubular structure with thickened walls in connection with the cecum inside the hernia sac. CT allows direct visualization of the appendix inside the inguinal canal, and in strangulated hernia, a blind ended tubular structure with bowel wall thickening, fat stranding, mesenteric engorgement and extraluminal fluid confined to hernia sac is seen.

In view of the rarity of AH, standardized treatment recommendations are lacking in literature. Whether or not an appendectomy should be done at the same time as hernia repair remains debatable. Losanoff and Basson addressed this dilemma and proposed a classification for AH, which could guide the type of surgical treatment offered[10] (Table 1). Our patient presented a AH Type 1, hence appendectomy was not done. However, in view of the presence of toxic fluid, mesh placement was avoided and darning done with non-absorbable suture.

The condition of the appendix determines the approach and type of hernia repair. If the appendix is normal, it can be reduced into the peritoneal cavity and a meshplasty done. Prophylactic appendectomy is better avoided.But, paediatric population has a higher risk of developing appendicitis. So, in children even a healthy appendix may be taken out. Moreover, the appendectomy will not alter hernia repair as mesh is not used in this population[10]. If appendix is inflamed or perforated, appendectomy with endogenous hernia repair should be done. No prosthetic material should be used, as appendectomy converts a clean surgery to a clean-contaminated surgery, thereby raising the infection rate and possible mesh infection[1,5].

Table 1— *Losanoff and Basson classification of Amyand Hernia*

Classification	Description	Management
Type 1	Normal appendix in an inguinal hernia	Hernia reduction, mesh repair, appendectomy in young patients
Type 2	Acute appendicitis in an inguinal hernia with no abdominal sepsis	Appendectomy through hernia, primary endogenous hernia repair, no mesh
Type 3	Acute appendicitis in an inguinal hernia with abdominal and abdominal wall sepsis	Laparotomy, appendectomy, primary endogenous hernia repair, no mesh
Type 4	Acute appendicitis in an inguinal hernia with concomitant abdominal pathology	Same as Type 3 + management of concomitant disease

Conclusion

AH is a very rare coexistence of two common disorders. As they are mostly diagnosed intra-operatively, the management plan is dictated by the condition of the appendix and age of the patient.

Source of support : None
Conflicting Interest : None

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Image in Medicine

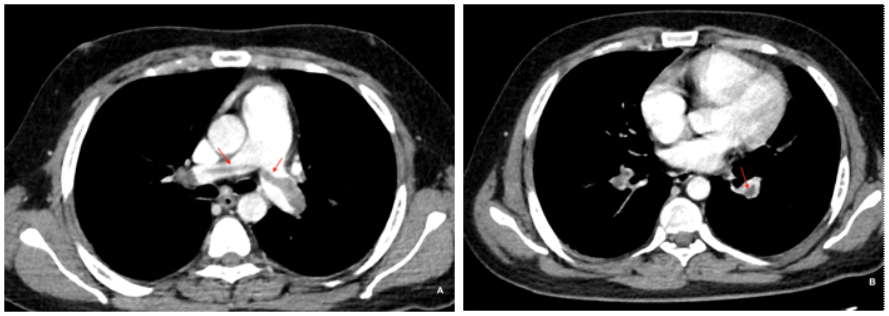
Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

A 46-year-old male presented with Acute Breathlessness since 2 days.

Questions :

(1) What is the diagnosis?
(2) What are the CT scan findings in Acute Pulmonary Emboli?



Answers :

(1) A large non-occlusive pulmonary embolus straddles the bifurcation of the pulmonary trunk, extending into the right and left pulmonary arteries - suggestive of saddle pulmonary embolism (Fig A).

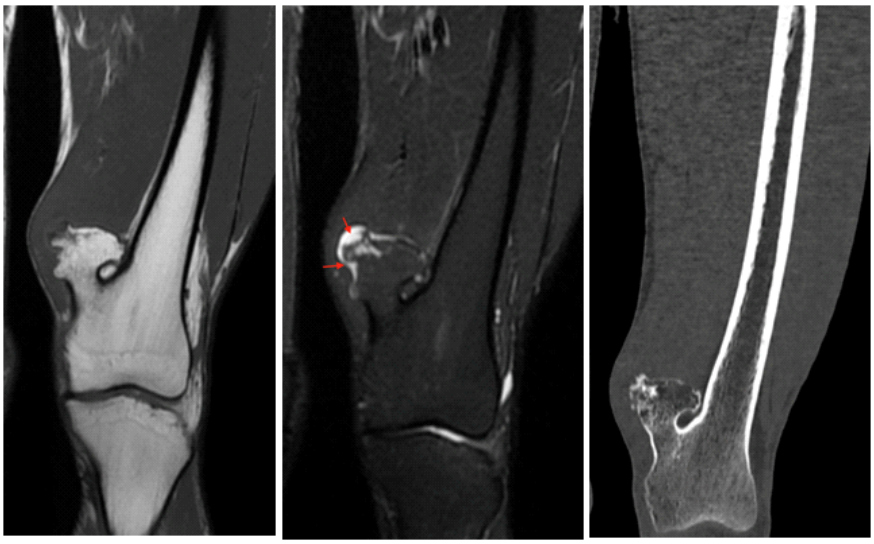
(2) CT pulmonary angiography will show filling defects within the pulmonary vasculature in cases of acute pulmonary emboli. When the artery is viewed in its axial plane, the central filling defect from the thrombus is surrounded by a thin rim of contrast, which is called the "Polo Mint sign" (Fig B).

Quiz 2

A 21-year-old male presented with Swelling around Left Knee Joint.

Questions :

(1) What is the diagnosis?
(2) What are the common locations of the lesion?
(3) What is the role of MRI?



Answers :

(1) Well defined pedunculated lesion with a thin cartilage cap (arrow) is seen in the metaphyseal region of medial aspect of left femur , which shows medullary and cortical continuation with underlying bone and projects away from the epiphysis. These imaging findings are suggestive of an osteochondroma (exostosis).

(2) Osteochondromas commonly arise from the appendicular skeleton, especially around the knee. The common locations are distal femur and proximal tibia.

(3) MRI is the best modality to assess the thickness of cartilage cap, the presence of edema in bone and visualizing neurovascular structures in the vicinity. A cartilage cap of over 15 mm in thickness after skeletal maturity is suspicious for malignant degeneration, while the cartilage cap upto 30 mm in thickness may be seen in young patients.

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Student's Corner

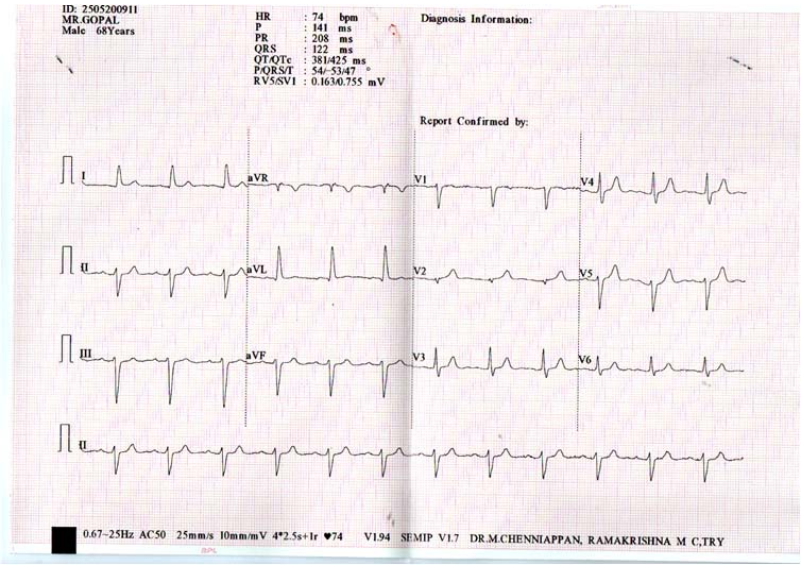
Become a Sherlock Holmes in ECG

M Chenniappan[1]

Series 8 :

"Confusion of Colours"

Routine ECG of 68 years old Male.



Questions :

(1) What are the ECG findings?
(2) Why is this Clue?
(3) What are the Practical Implications?

Answers :

(1) ECG FINDINGS :

This ECG shows sinus rhythm with left anterior fascicular block (LAFB) and PR interval in the upper limit. There is sudden appearance of Tall R wave in V3 (>V4) and sudden disappearance of R wave in V5. In V5 and V6 QRS complex is looking completely different. The unexpected appearance of R wave in one lead and sudden disappearance of R wave in another lead are suggestive of chest electrode malposition. Here electrode of V5 is placed in V3 position and electrode for V3 is placed in V5 position resulting in this unusual appearance and disappearance of R wave. This type of ECG change cannot be explained by electrocardiographic terms because the configuration of QRS in V5 and V6 is most often similar in normal ECG.

(2) CLUE :

The ECG technicians most often do the error of misplacing electrodes either in limb leads or in the chest leads. To avoid this error chest electrodes are given in particular colours. So that the technician remembers the particular colours for the specific electrode and place it in a correct place. The colours for the chest electrodes are

V1 - Red
V2 – Yellow
V3 – Green
V4 – Brown
V5 – Orange
V6 – Purple

These colours can be remembered easily by the following method.

Electrodes V1 – V3 remember traffic signals (Red, Yellow, Green)

Electrodes V4-V6 remember the pneumonic "BOP" (Brown, Orange, Purple).

In this simple way technicians can identify the chest electrodes and place it in the correct place without looking at the letter in the electrode like V1, V2, etc. In this ECG, orange is placed in Green position and Green is placed in orange position resulting in abnormal QRS complexes in V3 and V5.That is why the clue of "Confusion of Colours" is given.

(3) PRACTICAL IMPLICATIONS :

Correct ECG recording is an essential prerequisite for the right interpretation of Electrocardiogram. So, the ECG technician/paramedics who record the ECG should be taught how to connect the electrodes in the limbs as well as how to place chest electrodes in the correct positions. Most often technicians make error because they do not look at the name of the letters inscribed on that particular electrode and in a hurry, they misplace the chest electrodes. If they are taught the positioning of the chest electrodes as well as the limb electrodes through the colours it is easy for them to place the electrodes in a correct position. Some of this wrongly recorded ECGs may give a wrong diagnosis like dextrocardia, Myocardial Infarction, Ventricular enlargement etc and the patient may get inappropriate and incorrect treatment. So, educating the technicians in a simple way through colour coding of electrodes is an efficient method of making sure that the ECG is recorded properly.

[1]Adjunct Professor, Dr MGR Medical University, Tamilnadu; Senior consultant cardiologist, Tamilnadu; Ramakrishna Medical Centre, Apollo Speciality Hospital, Trichy

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Evaluating Contraceptive Use among Women in Gujarat, India

Sir, — India is a heavily populated country and efforts to control its population are being taken. However, it is surprising that even though most women in India know about contraception, and certain group (like young married couples) want to avoid pregnancy, the actual use of contraception is relatively low[1]. Patterns of contraceptive use are multifactorial but the sampling frame of this study is carefully chosen to overcome the variations in the population. This study aims to evaluate contraceptive usage among women of Gujarat, India to correlate its effects on number of the kids, number of unplanned pregnancies (Table 1). The correlation between contraceptive use and the level of education is explored.

Methodology : This study has been conducted in Ahmedabad, Gujarat. The questionnaire included questions of age, education status, marital status, whether sexually active or not, contraceptive used number of kids (Table 2) and number of unplanned pregnancies (Table 1). One-way ANOVA between contraceptives used and the number of unplanned pregnancies with Student Newman-Keuls Post HOC analysis. Similarly, one-way ANOVA between contraceptives used and the number of kids is shown in Tables with Student Newman-Keuls Post HOC analysis. Data analysis was done using IBM SPSS

Results : Total 320 responses were received. We see that there is a statistically significant association ($p<0.05$) between using natural methods or no contraception and a higher number of unplanned pregnancies. In Table 1 we can see that using no contraception or natural methods of contraception is linked ($p<0.05$) to a higher number of kids as shown in the Tables. A significant difference can be established between those using scientifically approved contraception when compared to those who used natural methods and no contraception.

Discussion : In India the major root cause of hesitancy has been established as the lack of awareness on correct use of contraception[2] and about the side effects that they can cause. The study further establishes the findings of many previous studies which show that level of education is positively linked to contraceptive use and negatively linked to fertility[3]. A silver lining must be that India is increasingly seeing a rise in contraceptive use by uneducated women[4], which helps progress the population control goals of the country.

In conclusion we can say that contraceptive use is an integral part of our population control goals. We should work towards shedding a light on its benefits and its drawbacks must be acknowledged and addressed.

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Table 1 — *Number of unplanned Pregnancies*

Student-Newman-Keuls[a,b,c]		Subset	
Contraceptive Used	**N**	**1**	**2**
Pills	27	0.11	
IUD	36	0.31	
Condom	58	0.43	
Natural methods	45		0.80
None	154		0.92
Significance		0.188	0.528

Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square (Error) =0.754.
(a) Uses Harmonic Mean Sample Size = 45.138. (b) The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed. (c) Alpha = 0.05.

Table 2 — Number of Kids

Student-Newman-Keuls[a,b,c]		Subset	
Contraceptive Used	**N**	**1**	**2**
Pills	27	1.11	
IUD	36	1.25	
Condom	58	1.29	
Natural methods	45		1.67
None	154		1.75
Significance		0.532	.637

Means for groups in homogeneous subsets are displayed. Based on observed means. The error term is Mean Square (Error) = 0.649.
(a) Uses Harmonic Mean Sample Size = 45.138. (b) The group sizes are unequal. The harmonic mean of the group sizes is used. Type I error levels are not guaranteed. (c) Alpha = 0.05.

JIMA, Vol 119, December, 2021

Sir, — We have read with interest the article byJanani Ramesh, *et al*[1]. We sincerely appreciate the effort of the authors to highlight the fact that thyroid autoimmunity in children and young adults with Type 1 diabetes and their siblings is common.

The authors have aimed to estimate TSH, fT4, Anti-TPO in T1DM children,T1DM sibling and Healthy control. 25% of the T1DM subjects had anti-TPO positivity where as in sibling 8.3% and in healthy control 6.7% had anti-TPO positivity. TSH level was also significantlyaltered among the groups but Ft4 level was not statistically different.

Recently we demonstrated[2] the level of different antibodies in T1DM subjects where we found 51% of T1DM subjects had anti TPO positivity and 25% of the subjects had anti-thyroglobulin (anti-TG) positivity.

There is a discordance in result between two studies but the reason for this is not well understood.

It would have been interesting if anti-TG level had been measured along with anti-TPO level, to better definethyroid autoimmunity.

Research Fellow — **Madhurima Basu**
Department of Endocrinology & Metabolism
IPGME&R, Kolkata

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COVID-19 Infection and Myocardial Infarction: Report of Two Cases from Eastern India

Sir, — The COVID-19 infection, caused by the SARS-CoV2 virus, has wreaked havoc all over the world over the past couple of years. Besides affecting the lung, this virus has also been found to have other fatal systemic manifestations. Although cardiac involvement like myocarditis has been reported, myocardial infarction is a very rare complication of this infection. Since the symptoms of Acute Myocardial Infarction (AMI), viz, chest pain, dyspnoea or arrhythmia can overlap with the clinical features of covid pneumonia and consequent hypoxia, it is often very difficult to differentiate the two merely on clinical grounds.

Case 1 :

A 76 year old male developed fever with acute dyspnoea. He was diagnosed to be COVID-19 positive and HRCT scan of thorax showed bilateral ground glass opacities (Fig 1). In view of the severe hypoxia (SpO_2 70% at 10 LPM oxygen), he was put on mechanical ventilation. However, on the second day of ventilation, there was sudden hypotension and refractory hypoxia. After ruling out pneumothorax by portable X-ray, an ECG was done, which showed (Fig 2) ST segment depression with T inversion in anterior leads. Troponin T level was strongly positive. Bedside echocardiography showed akinetic septum and parts of anterior wall. The patient was started on anti-platelet drugs, high dose statins and hemodynamic support was provided with noradrenaline infusion. Unfortunately, there was an episode of ventricular tachycardia on Day 4 and the patient suffered a fatal cardiac arrest.

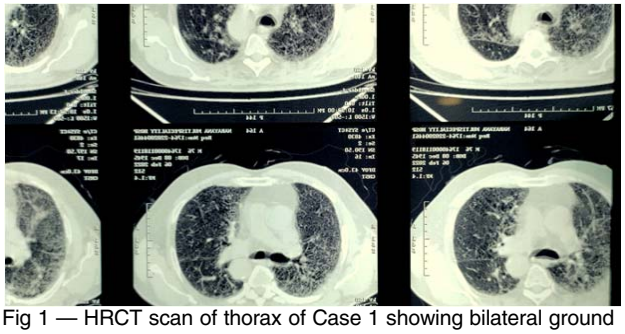

Fig 1 — HRCT scan of thorax of Case 1 showing bilateral ground glass opacities

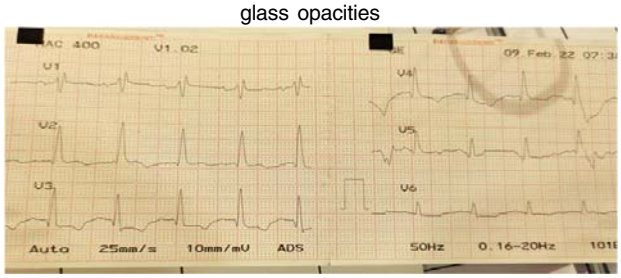

Fig 2 — ECG of Case 1 showing NSTEMI in leads V2-V5

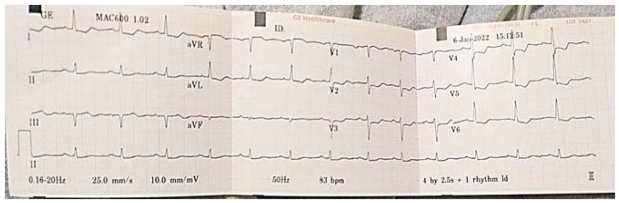

Fig 3 — ECG of Case 2 showing ST-T depression in leads V2-V6 and also I and avL

(Continued on page 70)

Case 2 :

An 80 year old diabetic man presented with pneumonia and hemoptysis. He was diagnosed as COVID-19 pneumonia and transferred to critical care unit. In view of his hypoxia, he was put on HFNO at 60/60 setting and he remained stable haemodynamically. On day 7 of critical care stay, the patient developed increasing hypoxia with cough. An ECG was done, which showed (Fig 3) ST-T changes in leads V2-V6, suggestive of NSTEMI. Troponin T was positive and echocardiography showed akinesia of entire anterior wall. The patient had to be put on mechanical ventilation and passed away after two more days.

The relation of COVID-19 infection with thrombotic complications is a matter of active research[1]. A direct causative effect of Covid infection on AMI is still a matter of debate. But scientists have come up with some plausible hypotheses in this regard. The COVID-19 virus targets the ACE2 receptors on endothelial cells and this may give rise to endotheliitis and consequent inflammation induced thrombosis[2]. While such inflammation mediated vascular obstruction has already been documented in the covid lung, whether a similar pathophysiology operates in the coronary arteries is still a matter of speculation. Transcriptome analysis of


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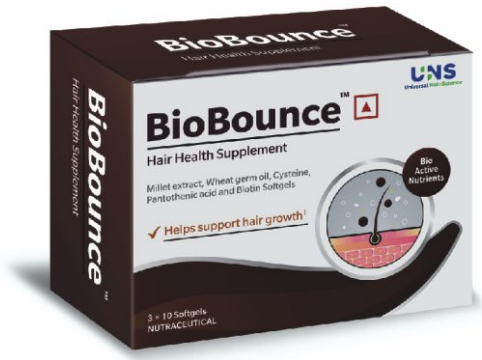

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