



Cohort Study

Is cancer significant comorbid condition in COVID 19 infected patients? -A retrospective analysis experienced in a tertiary care center in Eastern India



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ABSTRACT

Background: It was formerly thought that patients with a history of active cancer were more likely to acquire COVID-19; however, new research contradicts this belief due to the impact of economic stress, malnutrition, fear of hospitalization, or therapeutic discontinuation. A cohort-based study was undertaken in Indian regional cancer centre to understand cancer-covid link in patients.

Method: A total of 1565 asymptomatic patients were admitted based on thermal screening and evaluation from the screening form from June 2020 to November 2020. The RT-PCR technology was used to assess the COVID 19, and patients who tested positive for COVID 19 were transported to a hospital designated by the government for COVID 19 patients. Patients who tested negative for the COVID 19 virus were transferred to the normal cancer unit to complete their treatment. Patients who tested positive for COVID 19 were referred to the COVID hospital, where their findings were analyzed and correlated with patient age, gender, and cancer stage.

Findings: Out of 1565 patients, 54 patients (3.4%) tested positive. Most of the patients are in 45–59 years age group. As female patients admitted were more in number than males, so predominance of disease is higher in female. 3 patients were symptomatic after admission and 2 were severe and were admitted to the ICU with ventilations. 8 patients died in Cancer and one patient died in COVID 19.

Interpretation: As only 3.4% patients tested positive and only one patient out of 54 had died, so cancer is found not to be a comorbid condition towards COVID 19 patients in the Indian population studied.

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1. Introduction

The first case of COVID 19 was discovered by World Health Organization (WHO) in the month of December 2019 in Wuhan, China and COVID-19 was designated a "Public Health Emergency of International Concern (PHEIC)" by the WHO on January 31, 2020, and a "pandemic" by the WHO on March 11, 2020 [1]. The fast spread of positive sense single stranded RNA Virus, SARS-CoV-2, coupled with a worldwide lockdown, has impacted healthcare systems. Patients' treatment and safety have worsened as a direct result of inadequate infrastructure and human resources in the health care system. The situation is made much more difficult as a consequence of severe disruptions in the supply chain as well as widespread concern among patients and people working in the healthcare profession. This makes the situation far more difficult.

SARS-CoV-2, the causative agent of corona virus infection, belongs to the CoV group of viruses enveloped in lipid membrane obtained from host cell in which the viral surface proteins (such as spike protein) are embedded. Apart from the nonstructural protein RdRp (RNA-dependent RNA polymerase) the viral RNA codes for nucleocapsid protein bordering the RNA genome and three membrane proteins such as S-glycoprotein, matrix protein & envelope protein. The S-glycoprotein can attach to the angiotensin converting enzyme 2 receptor (ACE2) located in the lower respiratory tract of humans. Beside homologous recombination, the diverse nature of CoV is also driven by high mutation rates mediated by error prone RdRp responsible for duplication of genetic information [2].

The transmission of SARS-CoV-2 can occur via several routes, through direct physical contact or indirectly through fomites having droplets more than 20 μm in diameter and are accumulated in the conjunctiva of vulnerable host, aerosol transmission mediated by respiratory droplets having diameter less than 10 μm accumulated in the alveolar region. The virus enters the host cell by fusing its envelope with host cellular membrane mediated by their spike protein capable of undertaking structural rearrangements. Once inside the host binding of S-protein to ACE2 drives the life cycle of SARS-CoV-2 [3].

It is thought that patients who have many ailments at the same time are more prone to suffer from viral infections [4]. People having a history of malignancy, particularly lung cancer, were shown to have an increased risk of contracting COVID-19 and its consequences [5–7].

M1 macrophages have been demonstrated to be activated in COVID-19 disease. This activation of M1 macrophages is associated with MAS, cytokine storm, lymphopenia, endothelial injury, and a rise in intravascular blood coagulation [8]. Cancer, on the other hand, stimulates the activation of M2 macrophages, which suppress immune responses while also contributing to tumor development. As the cancer patients are immuno-suppressive, the susceptibility towards the virus among cancer patient population is higher [8].

In a recent study, cases of COVID-19 were collected and analyzed from 575 hospitals spread throughout 31 Chinese regions. 18 of the total patients had a prior cancer diagnosis, suggesting that the incidence of cancer in China is greater than in the overall population (0.9% vs. 0.29%). It was also shown that post chemotherapy or post-surgery individuals had a greater likelihood of experiencing more severe episodes, as per clinics, than individuals, those who didn't get these therapies. This was discovered in contrast to people who did not get these cancer therapies. As this result came out from cancer population which is small in size, so as a limitation, it's tough to conclude a judgment. The research was carried out on cancer patients [5].

The meta-analytical investigation based on 512 published articles and 13 studies, involving a total of 3775 COVID-19 individuals, 63 (1.66%) with Cancer and 3712 (98.3%) without cancer, revealed that the cancer patients were older than the entire data group (63 years vs 48.7 years). In five investigations, 50.8 years (SD.3) is the mean age of 1862 patients. In 12 research, 58% of the participants were men, while 42% of the population consisted of females [9].

Organizations like as the American Society of Clinical Oncology

(ASCO), the Centers for Disease Control and Prevention (CDC), and others have published guidelines to address risk mitigation, patient care prioritization, virtual care, health care team management, treatment of cancer patients undergoing surgery, systemic therapy, radiations, clinical research [CR], and recovery planning. The practice of deferring surgery for possibly treatable early cancers is a significant point of contention among the recommendations [1]. COVID 19 breast cancer consortium has suggested that a delay of 6–12 weeks in surgery, will not affect the outcome [10]. According to the guidelines followed by some of the government funded cancer hospitals are establishing screening camps outside the hospital, strict control and restrictions of relatives in the OPDs and IPDs and also establishing a fever clinic and isolation wards and maintaining a rotational duty schedule to prevent the medical system from a mass quarantine [11].

An immunosuppressive environment, which is a core characteristic of malignancies and plays a crucial role in disease progression, is caused by incorrect immune cell growth. This atmosphere is crucial in the progression of the sickness. This is the primary factor that contributes to the immunosuppressive environment [12]. Comorbid disorders such as cardiovascular disease, high blood pressure, chronic obstructive pulmonary disease, chronic renal disease, diabetes and cerebrovascular sickness are expected to reduce macrophage functions and lymphocyte function, thus reducing the immunity, and contribute towards the severity of COVID 19 [13].

Previous studies found that cancer patients usually have these comorbidities like hypertension, Diabetes, Cardiac disease, cerebrovascular disease, chronic liver disease, chronic renal disease and chronic lung disease (13). Patients with persistent respiratory difficulties, such as chronic obstructive pulmonary disease, are more prone to develop acute respiratory distress syndrome because they have a lower resistance to the virus (ARDS). It produces an inflammatory infection in diabetics by causing an increase of activated innate immune cells in metabolic organs, which leads to the generation of inflammatory mediators, most notably IL-1 and TNF- [13].

Hematological malignancies were found to be the most prevalent kind of cancer that was reported among COVID-19 patients, according to a meta-analysis that included 181,323 individuals from 26 studies including 23,736 cancer patients as well as a systematic evaluation of 31 research. This was followed by head and neck cancers (9.6%), breast cancers (29.2%), lung cancers (23.7%), gastrointestinal malignancies (15.2%), prostate cancers (11.1%), and gynecological cancers (15.2%). Cancer of the head and neck (2.63%). The mortality rate from hematological malignancies was the highest in hospitals, coming in at 33.1%, followed by the death rate from lung cancer, which came in at 28.0%, gastrointestinal malignancies, which came in at 19.8%, and breast cancer, which came in at 10.9% [14].

It was also observed that chemotherapy was the most often used treatment modality in cancer patients with COVID-19 (30.3%), followed by hormone therapy (17.4%), targeted therapy (15.4%), radiation (13.8%), immunotherapy (9.1%), and surgery (7.3%) [14]. To combat the COVID-19 pandemic, the American Society of Clinical Oncology (ASCO) held a global webinar to emphasize the importance of preventing infections, providing timely and appropriate care, minimizing harm from interruptions in care, and being ready for an increase in the number of new COVID-19 cases, complications, or comorbidities [14]. In this hospital based retrospective study 1565 patients have been enrolled from June 2020 to November 2020 out of which 54 (3.4%) patients were positive. During admission they were asymptomatic and it has been tried to make a correlation between COVID 19 and Cancer.

2. Methods

2.1. Study design

In a tertiary care hospital situated in eastern India, a total 1565 asymptomatic patients (during admission) were enrolled in this study

from June 2020 to November 2020 in the pre vaccination era. The patients were admitted on the basis of thermal screening and evaluation from the screening form. High temperature, symptoms of COVID 19, travelling history in last 14 days are excluded from the study. All the patients (COVID 19 positive or Negative) were asymptomatic during admission and admitted in the 40 bedded isolation ward for treatment after RT PCR to check whether the patient has SARS-COV 2 positive or not. The COVID 19 has been checked by RT-PCR method and the COVID 19 positive patients have been transferred to government allocated COVID 19 hospital.

The COVID 19 negative patients are transferred to general ward from isolation ward for the further cancer treatment. Hospital followed standard procedures to limit any hospital infection among patients, health care professionals and caregivers through PPE, disinfectants etc. Institutional Ethical Committee of Chittaranjan National Cancer Institute has approved the study (IEC approval no: CNCI-IEC-KKM-11). The work has been reported in line with the STROCSS criteria [24].

RT-PCR based detection of COVID: BSL-2 labs were set up to handle patient samples and conduct RT-PCR testing. SARS nCoV-2 or Covid 19 testing was performed according to the guidelines of Indian Council of Medical Research (ICMR). Briefly, both oropharyngeal and nasopharyngeal swabs were collected and transported in Viral Transport Medium (VTM) to our laboratory. For each sample, 140 µl of VTM was used for extraction using HiPure Viral RNA Purification kit (HiMedia labs, India) according to the manufacturer’s instructions. The extracted RNA was measured by Nanodrop 2000 for estimating the quality of extracted RNA by 260nm/280 nm 5 µl of extracted RNA was used for SARS nCoV-2 testing using different kits including Taqpath Covid19 multiplex real time RT-PCR kit (Thermo,USA), ViralDetect2 multiplex real time PCR kit for Covid 19 (Genes2Me,India), Diasure nCoV19 detection assay (GCC Biotech, India), MerilCov19 One Step RT-PCR Kit (Meril Diagnostics, India) approved and supplied by ICMR to our laboratory. In all the kits, E gene, RdRP or Orf1ab, N gene were used for detection and RNaseP was used as a housekeeping gene. RT-qPCR was run according to the manufacturer’s guidelines. Positive, Negative and Inconclusive samples were reported according to the kit manufacturer’s guidelines based on the PCR run. Validation was performed biannually according to the ICMR guidelines by Intra-laboratory testing and by External Quality Assurance Program (EQAS) as provided to us by ICMR. All the samples for validation were in 100% concordance with the intra-laboratory report and the EQAS report. In general, sensitivity and specificity of the kits were not mentioned in the kit literature.

2.2. Patient based observational study

2.2.1. Inclusion criteria

1. Asymptomatic Cancer Patients with no high fever and no recent history of travelling within 14 days of hospital admission screening.
2. Age more than 18 years (18–75 years)

2.2.2. Exclusion criteria

1. If any family member is COVID 19 positive.
2. Very advanced or Terminal Cases.

Basic health criteria of patients from physical measurements were carried out for hospital admission. Basic comorbid conditions for both cancer or covid were considered.

2.2.3. Statistical analysis

For the purpose of carrying out the Statistical Analysis, the computer application known as Epi Info (TM) 7.2.2.2 was used. The EPI INFO acronym has been formally adopted as the trademark of the Centers for Disease Control and Prevention (CDC). In order to calculate the means as well as the standard deviations that related to them, a descriptive

statistical analysis was carried out (S.D.). A test of proportion was used to analyses the discrepancies between the proportions, and the result of that test was used to determine the Standard Normal Deviate (Z). In order to make a comparison between the two means, a t-test was carried out. When p was found to be less than 0.05, it was presumed that statistical significance existed.

3. Result

RT-PCR positivity: 54 Patients (3.4%) were found to be COVID-19 positive among 1565 patients admitted and associated with different degrees of viral load as observed by expression of marker genes.

Correlation of Patient age, gender and cancer stages with treatment outcomes: Patient age, male-female ratio, t-test value and cancer stages were studied and statistically correlated with outcomes in terms of COVID-19 along with respective CT value (Table- 1-6, Figure-I, II).

The mean age (±S.D.) of the patients was 50.38 ± 10.82 with range 18–71 years and the median age was 49 years. Most of patients who got admitted in the hospital are at the age group of 40–60 years (Fig-IA). 74.0% of the patients were of age ≥45 years which was significantly higher than other ages (Z = 6.78; p < 0.0001). Thus, in this study COVID-19 infection was more prevalent among the patients with age ≥45 years (Table-2).

The ratio of male and female (Male: Female) was 1.0:3.6. Proportion of females (74.1%) was significantly higher than that of males (25.9%) (Z = 6.78; p < 0.0001) (Fig-IB). During admission more Female patient got admitted than male patient (Table-2).

Though the mean age of the females was lower than that of the males, t-test showed that there was no significant difference between them (t₅₂ = 1.06; p = 0.30). However, females were at risk of having COVID-19 at younger age than males (Table-3).

94.4% of the cases were asymptomatic which was significantly higher than symptomatic cases (5.6%) (Z = 12.44; p < 0.0001). (Table-4), (Fig. 1C). In only 3.7 of the cases ITU admission was required. (Table-4). In only 3.7% of the cases ventilation was required as respiratory support. (Table-4), (Fig-ID). 83.3% of the cases were discharged alive which was significantly higher than the patients died during treatments (16.7%) (Z = 9.33; p < 0.0001). A female patient aged 43 years died due to COVID-19. (Table-5), (Fig-IE).

Comparative value of the three genes namely E gene, Orflab, RdRp used in CT value measurement among the patient study sample. Mean value of: E gene: 24.89189189, Orflab: 26.10810811, RdRp: 26.4. Standard deviation of: E gene: 5.440505, Orflab: 6.008253, RdRp: 5.882176 (Fig. 2A).

Percentage of patients having CT value below or 25 and above 25

Table 1
Types of cancer and staging and number of patients.

Cancer	Staging	Number of COVID positive patients
CA Ovary	IIIB	8
CA Rectum	IIIB	3
CA Ovary	IIIC	5
CA Cervix	IIIB	2
CA Stomach	IV	3
CA Breast	IV	7
CA Breast	III B	9
CA Esophagus	III B	1
CA Mouth	IIIB	2
CA Peritoneal	IIIB	1
CA Periapullary	IV	1
CA Endometrium	IV	2
CA Sigmoid Colon	IIIB	1
CA Testis	II	1
CA Thyroid	II	1
CA Lung	IIIB	4
Sarcoma	Post-Surgery	1
NHL	IIIB	2

Table 2
Age and Gender of Covid positive patients.

	Age				Gender	
	<30	30–44	45–59	≥60	Male	Female
Covid positive	1	13	28	12	14	40
% Covid Positive patients	1.9%	24.1%	51.9%	22.1%	25.9%	74.1%

Table 3
Age and gender of the patients.

Age (In years)	Gender		t-test	p-value
	Male	Female		
Mean ± SD	52.57 ± 10.62	49.62 ± 10.92	1.06	0.30 NS
Median	52.5	48.5		
Range	32–69	18–71		

Table 4
Symptoms, Requirement of ITU and Requirement of Ventilation of patients.

Symptoms of the patients		Requirement of ITU admission of the patients		Requirement of ventilation as respiratory support	
Present	Absent	Required	Not Required	Required	Not Required
3 (5.6%)	51 (94.4%)	2 (3.7%)	52 (96.3%)	2 (3.7%)	52 (96.3%)

Table 5
Status of health of the patients at discharge.

Status of health	Number	%
Discharged alive	45	83.3%
Died due to cancer	8	14.8%
Died due to COVID-19	1	1.9%
Total	54	100.0%

Table 6
Percentage of patients having CT value 25 or below and above 25.

CT value	% Of patients having CT value 25 or below 25	% Of patients having CT value above 25
E gene	51.35	48.64
Orflab	40.54	59.45
RdRp	34.28	65.71

signifies the viral load. In the study it was seen that percentage of patients having CT value above 25 was more. (Fig-IIB) (Table-6).

4. Discussions

COVID-19 has been linked to an inflammatory response, oxidative stress, and other pathophysiological problems. All of these pathophysiological anomalies have the potential to have a significant impact on cancer diagnosis and treatment choices [15–18]. Research was done in retrospect discovered that even in moderate cases of COVID-19, there were substantial increases in the levels of several blood cancer indicators as compared to normal control patients. Compared to the general population, the prevalence of these cancer markers was significantly higher in individuals with severe COVID-19 [16]. As a result of these alterations, the positive and negative predictive values of a range of biomarkers linked to tumors may change, making it more difficult to effectively detect and identify cancer, as well as disease progression and treatment choices [19].

In our study, the 1565 patients were admitted in the hospital 40

bedded isolation ward through a screening process. In the isolation ward, COVID 19 testing was done in CNCI Rajarhat Campus and 54 patients (3.4%) were tested COVID 19 positive. All the patients were asymptomatic during admission.

There are many advantages of testing for COVID-19 before initiating systemic medication. To begin, the diagnosed patient may be excused from undergoing immunosuppressive medication, which has the potential for major side effects. The patient may then be referred to an infectious disease (ID) expert for further examinations. Contact tracing is also important for the prevention purpose [20].

A substantial case fatality rate was seen among individuals who initiated medication less than four weeks after the beginning of their symptoms, according to the results of a retrospective research done in China on 205 cancer patients infected with COVID-19 [21]. In an UK based observational study it was noted that death was unrelated to chemo [22]. According to the Tata Memorial Hospital-COVID-19 working group, systemic thinking, a climate that encourages healthy disagreements, quick multipronged execution, readiness to modify choices on short notice, excellent communication, and collaboration are all essential to control this pandemic [23].

This is one of the first study in India in a Government Setup where a large number of asymptomatic patients had undergone COVID 19 testing. This study has shown that only 3.6% of patients were COVID 19 positive. According to our study, this can be stated easily that Cancer is not a comorbid situation towards COVID 19 affected patients. Only 3.4% patients were tested positive and only 3 patients out of 54 were symptomatic, 2 patients were severely symptomatic and those patients had been admitted to ITU with ventilation support. Out of 54 patients, only one patient died in COVID 19. Another Indian Study have also shown similar scenario where 1.45% patients were COVID 19 positive. So, it can be stated that in Indian genetics and environment, COVID 19 is not a Comorbid situation.

5. Conclusions

Our retrospective single center study in regional cancer center showed the following outcomes in cancer patients-

- 54 patients out of 1565 have been COVID19 positive i.e. (3.4%) COVID Positive
- Over 45 years old patients are more venerable on the basis of this study result
- Females are more affected than male.
- Majority of patients (94.4%) were asymptomatic and 5.6% patients were symptomatic after the admission
- ITU admission was not needed for 96.3% patients and ITU admission was done in 3.75% patients. These 3.75% patients were in ventilation.
- 83.3% patients were discharged alive, 14.8% patients died due to cancer and 1.9% patients died due to COVID 19
- Our study cohort represented that cancer is not a comorbid condition in COVID-19 infected patients where other comorbid conditions remaining almost same.

Limitations

- It's a single center study [It's a regional cancer center covering the eastern region of the study], so, the population is limited.
- Hematological malignancies are less in number
- We have included only the asymptomatic patients (not in their end stage of cancer) and the patients without recent travelling history in the study.
- Number of female cancer patients are more than male because the admission of the gynecological cancers are high at that time in the institute.
- Most of the patients admitted in the age group of 40–60 years

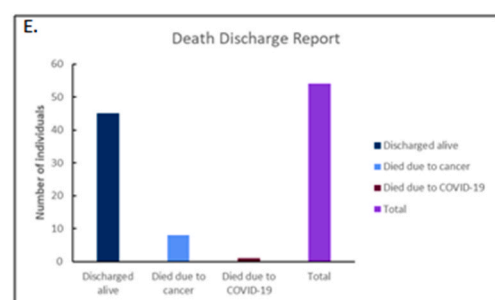
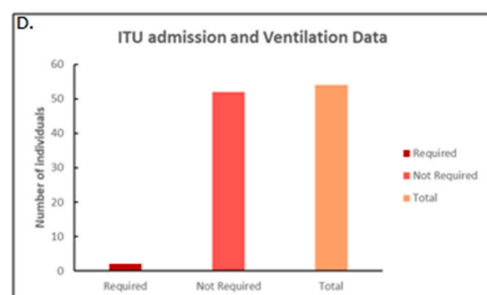
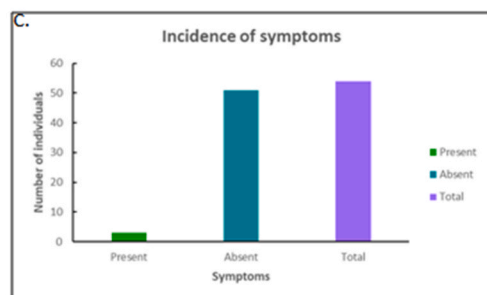
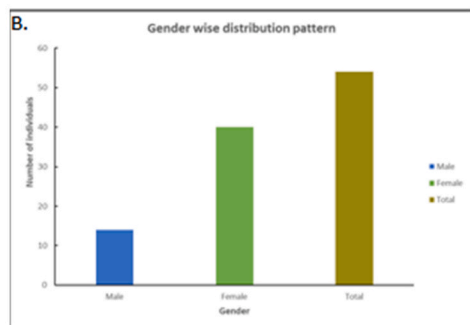
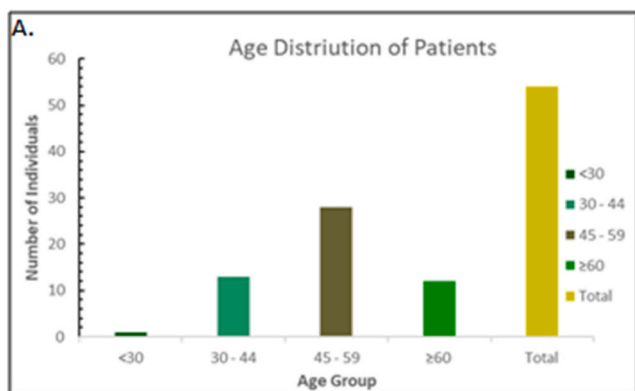


Fig. 1. A: The Bar Graph shows the maximum affected age group is 45–59 years. In the hospital most of the patients got admitted with an age group of 40–60 years. B: Shows Females are more affected than male (Females are more admitted than Male). C: Shows that most of the cancer patients are asymptomatic during and after the admission. D: Shows majority of the patients didn't go to moderate to severe stage, So, ventilation or ITU setup wasn't a need. E: Shows most of the patient have discharged alive. Only 1 patient died due to COVID19 and 8 patients died due to Cancer.

Ethical approval

Ethical Committee of Chittaranjan National Cancer Institute has approved the study. IEC Ref: CNCI-IEC-KKM-11.

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Specific author's contribution

Conceptualization: Dr Kalyan K Mukherjee; Covid control Strategy: Dr. Aniruddha Dam, Dr. Deepa Chakrabarti, Dr. Debasish Jatua, Dr. Saubhik Sengupta, RT-PCR Lab: Dr. Saubhik Sengupta, Dr. Sankar Sengupta.

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Radiology Support: Dr. Suparna Majumdar.

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Institutional Support: Dr. Sankar Sengupta, Dr. Jayanta Chakrabarti.

Declaration

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Registration of research studies

1. Name of the registry: Institutional Ethical Review Committee
2. Unique Identifying number or registration ID: IEC Ref: CNCI-IEC-KKM-11
3. Hyperlink to your specific registration (must be publicly accessible and will be checked):

Guarantor

All the authors are responsible towards this research work.

Consent

Patient's privacy is fully maintained. Authors haven't disclosed any identity of the patients in the manuscript.

Provenance and peer review

Not commissioned, externally peer reviewed.

Declaration of competing interest

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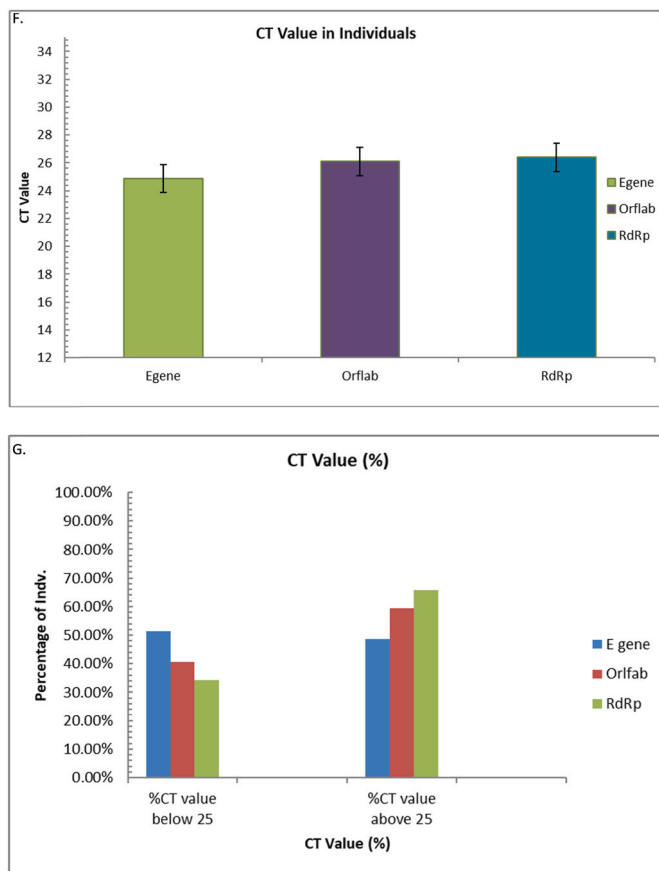


Fig. 2. A: Comparative value of the three genes namely E gene, Orflab, RdRp used in CT value measurement among the patient study sample. B: Percentage of patients having CT value below or 25 and above 25.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amsu.2022.104248>.

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