

Survival analysis to assess the length of stay of novel coronavirus (COVID-19) patients under Integrated Medicine - Zinc, Vitamin C & Kabasura Kudineer (ZVcKK)

Retrospective Study to assess the length of stay of novel coronavirus (COVID-19) patients in GMC & ESIH Coimbatore who were under- Integrated Medicine -Zinc, Vitamin C & Kabasura Kudineer (ZVcKK)

D.Jamuna¹, P. Sathiyarajeswaran², M. S. Shree Devi³, K. Kanakavalli⁴,
N. P. Vinod⁵, A. Nirmala⁶, T. Ravikumar⁷, P. Pathiban⁸, K. Babu⁹, C. Dhanam¹⁰

¹Assistant Medical Officer, Siddha Government Medical College & ESI Hospital

²Assistant Director, Director i/c, Siddha Central Research Institute, Chennai

³Research Officer (Siddha), Siddha Central Research Institute, Chennai

⁴Director General, Central Council for Research in Siddha, Chennai.

⁵Statistical Assistant, Siddha Central Research Institute, Chennai

⁶Dean, Government Medical College and ESI Hospital (GMC & ESIH), Coimbatore

⁷Medical Superintendent, GMC & ESIH, Coimbatore

⁸Joint Director, Commissionerate of Indian medicine Chennai.

⁹Assistant Medical Officer, Ayurveda Government Medical College & ESI Hospital

¹⁰District Siddha Medical Officer, Coimbatore.

e-mail: shreemd@gmail.com

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Ethical approval: "For this type of study consent is obtained."

The personal identifiers such as name and address of the patient's records were removed to ensure the confidentiality and anonymity. Collection of information regarding the age, gender, address, and all other information collected from patients were also kept confidential and as this study is a data observation gone for ethical committee approval.

Ethics committee of GMC-ESI – Coimbatore – No: 20911/2020.

Informed consent: "For this type of study formal consent is obtained."

Abstract: Objective: COVID19 pandemic out of all odds has created an opportunity to offer treatment in an integrative manner. This study measures the Length of stay (LS) of patients in an integrative way as done earlier in China and Vietnam. Length of stay,

Clinical presentations, and Comorbidities were analyzed among COVID19 patients in ESI Hospital, Coimbatore, Tamil Nadu, India.

Method: Retrospective cross-sectional data on 251 Positive COVID19 patients of both sexes irrespective of age admitted from 27 March 2020 and 26 April 2020 cases were included in the study. The final discharge date is taken as 5th May 2020. Kaplan Meier survival analysis was adopted.

Results: Male, female ratio were 141(56.2%): 83(33.1%), 12 (4.8%) Male Child and 15 (6.0%) were Female child. 5.2% of the patients were in the age group greater than 60, 75.3% were in the age group 20-60, and the remaining 19.5% were 0-20 age group. 84.9% of patients were Asymptomatic, while fever and cough were the main symptoms recorded in the remaining cases. CT scan was done for 7 patients. No mortality and no serious adverse events were reported. Comorbidity is 15% and does not influence hospital length of stay. The overall median length of stay is 12 days for those who were under ZVcKK (Median ST CI- 11.59-12.41).

Conclusion: This study recorded a median of 12 days in the Length of stay and 13.5 days in the Length of stay average. Comparing earlier studies, patients taking ZVcKK have savings of 7 days. i.e., the relief speed is higher while using ZVcKK.

Keywords: COVID-19, Integrated Medicine, Vit.C and Zinc tablets, Kabasura Kudineer, Kaplan Meier survival analysis, Siddha Medicine.

1. INTRODUCTION

Following the first-ever reported case in Wuhan in December 2019, PHEI (Public Health Emergency of International concern) was announced by WHO in January [1]. SARS-CoV-2 has spread widely across all continents; as of the latest situation report on August 16, 2020, by WHO, a total of 21, 294, 845 cases with mortality of 7,61, 779 have been reported [2]. There are 2 647 316 cases in India and 51,045 deaths as of August 16, 2020; these data represent the imminent risk facing the country [3]. India declared an emergency alert in March 2020. Transmission of virus spreads via physical contact with infected individuals, contaminated surfaces, and droplets [4]. COVID-19 commonly reported symptoms are fever, vomiting, chills, headache, dyspnoea, nausea, sore throat, coughing up blood, shortness of breath, myalgia, diarrhea, and malaise. The severe infection leads to pneumonia, acute respiratory distress syndrome (ARDS), and sometimes multi-organ failures such as kidney failure and even death [5]. With its strong internal and external medications, the lineage of Siddha medicine has been in vogue to treat viral diseases [6]. At Present, treatment aspects are isolation and treating symptoms stands as the only option or vaccine therapy Due to the non-availability of proved therapies. Therefore, it is necessary to develop a treatment for COVID-19. Based on the Siddha system of Medicine advisory given by the Ministry of AYUSH, India for COVID-19 mentioned stages of medicines for treatment, prophylaxis, and related convalescence. Kabasura Kudineer (KSK) found its place in the advisory of the Ministry of AYUSH [7]. The Tamilnadu government advocates zinc and Vitamin c. Administration of CBE – ESI took a positive step to contain Covid19 through Integrated approaches. In this regard, the benefit offered by Integrated Medicine -Zinc – (150 mg),

Vitamin C – (500 mg) & Kabasura Kudineer (ZVcKK), and the association between Average lengths of Stay in the hospital is evaluated. Siddha medicine is one among the traditional medicine originated on par with Ayurveda and recognized by WHO in India with its origin of centuries-old [8]. Efficacy of Siddha medicines was documented in earlier pandemics like HIV and epidemics like Chikungunya, Dengue, and Swine flu influenza outbreaks [9]. During Dengue outbreaks and post-mitigation Chennai floods, Nilavembu Kudineer is used extensively to prevent infection [10]. Nilavembu Kudineer has been used to mitigate Dengue, Kabasura Kudineer has been used at Swine flu epidemic. These two drugs are repurposed and found their place in the AYUSH Advisory. Kabasura Kudineer has been recommended by Tamilnadu Govt. to encounter COVID -19 under Aarogyam scheme. Kabasura Kudineer is one such concoction mentioned in the Siddha manuscript Citta Vaittiyattirattu [11], one of the books listed under the Drugs and cosmetic act [12]. It's a combination of fifteen herbs cultivated, collected, procured, and authenticated by a Pharmacognostic professional. After the purification process, this compound formulation is made into a coarse powder, which is used to prepare the concoction having a shelf life of three hours. (After three hours it is not consumable as it denatures itself, concoctions expire after three hours). Kabasura Kudineer is one of the drugs included in Advisory of Govt of India, released by the Ministry of AYUSH for symptomatic management of Covid 19 [7]. Initial studies using in silico model supported the efficacy of drug inhibiting SARS- CoV2 main protein. Govt of Tamilnadu, in its Aarogyam scheme, introduced this drug and also permitted studies involving asymptomatic and mild cases [13]. Kabasura Kudineer is a Sastric Siddha Medicine used in Slethuma Suram equated to the indicated COVID -19 like illness [11]. It is polyherbal formulation consists of fifteen Siddha Herbal drugs mixed in equal proportion. Approximately 5gms of coarse powder boiled in 240ml of water until it reduces to one-fourth of its quantity Consume 30 to 60 ml of twice or thrice daily. The ingredients in the above Siddha formulation are absorbable when administered orally [11]. COVID-19 is a new strain of coronavirus that has not been previously identified in humans. The COVID-19 is the cause of an outbreak of respiratory illness first detected in Wuhan, Hubei province, China. Coronaviruses are a large family of viruses known to cause illness ranging from the common cold to more severe diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).

A confirmed case was defined by epidemiological history and/or clinical features that a suspected case may contact with COVID-19 infected persons and/or had symptoms and signs of COVID-19 infection, plus positive laboratory tests including virus nucleic acid, gene sequencing, and serum antibody detection.

1.1 ETHICS

Personal identifiers such as name and address of the patient's records were removed to ensure confidentiality and anonymity. The collection of information regarding age, gender, address, and other information collected from patients was also kept confidential. This study is a data observation and gone for ethical committee approval (IHEC Approval Number: 20911). Consent obtained from the participants.

2. METHODS

Data collected from confirmed COVID-19 cases admitted in GMC & ESI Hospital Coimbatore. Collected information on personal comorbidities, Travel history, and the length of hospital stay for confirmed patients. We conducted Kaplan Meier survival analysis for result interpretation. KSK (Kabasura Kudineer) was given daily after food for Adults- 60 ml and Children – 15 ml for all participants. Tested the equality of hospital stay length is the same for different parameters using a one-way analysis of variance. And there are statistically significant differences; hence to study the equality of survival curves, the Kaplan -Meier (KM) method to estimate overall survival (OS) time is used for the analysis [14-15]. Data were analyzed using SPSS software.

2.1 STATISTICAL ANALYSIS

The relationship between patient's age, gender, the time interval from illness onset to diagnosis, hospital-grade of patients, clinical grade, and the length of hospital stay after admissions for confirmed patients were compared and analyzed by survival analysis. The event of interest is discharge status; 0 for no discharge, 1 for discharge, and death are treated as 0. The Kaplan-Meier method was used for single factor comparison. In our study, no death is reported.

2.2 SURVIVOR FUNCTION

Survivor function gives a chance for a patient to survive a specific point of time (t). $(S(t) = P(T > t))$ [16].

2.3 COMPARISON OF SURVIVOR FUNCTIONS

Wilcoxon test or Breslow test effectively compared to, or more survivor functions in survivor studies other than this log-rank test are used in large sample studies. This test compares the observations with that of the expected number of events, whereas per the null hypothesis, all the comparisons are the same. Comparisons are direct proportion with a time point and an event observation. Here each ranked item is compared with every ranked value in another group.

3. RESULTS

Out of the 251 COVID Positive cases, 151(60.2%) had close contact with positive cases, 94(37.4%) had travel history through containment zone like Delhi, and one person 0.4% had a travel history to Kashmir and only the remaining 5(2%) were free from travel history. Duration of hospital stay varies from 1-36 days. 5.2% of the patients were in the age group greater than 60, 75.3% were in the age group 20-60, and the remaining 19.5% were 0-20 group (Table 1).

Age Group	Frequency	Percent
0-10	21	8.4
11-20	28	11.2
21-30	51	20.3
31-40	62	24.7
41-50	44	17.5
51-60	32	12.7
61-70	8	3.2
71-80	3	1.2
81-90	2	0.8
Total	251	100.0

Table1: Age Group Category

During the one-month admission period, a total of 251 positive cases were admitted in the hospital is included in the study. Out of which 141(56.2%) were male, 83(33.1%) were female, 12 (4.8%) Male Child, and 15 (6.0%) were Female child (Table 2).

Gender	Frequency	Percent
M	141	56.2
F	83	33.1
MC	12	4.8
FC	15	6.0
Total	251	100.0

Table2: Gender Distribution

84.9% have admitted with no symptoms, or the symptoms are not recorded; in the remaining cases, fever and cough were the main symptoms recorded. During admission, 13 (5.2%) have a fever, 22(8.8%) have cough, 2(0.8%) have both fever & cough, 1 (0.4%) with Cough & Respiratory Distress and remaining 213(84.9%) have no such symptoms. An abdominal CT scan of 7 patients was done during the study period. 6 of them have GGO (Ground glass opacities), and one shows normal in the result. After the study period, it reduced by 3 have GGO, and all others are turned to be normal. 85 years old patient got cured of COVID 19, but showing Opacity in both CT and X-ray and is referred to CMC Hospital Vellore district. Her Length of hospital stay is 18 days. While testing the equality of hospital stay length is the same for different parameters using a one-way analysis of variance, like symptoms, travel history, gender, all variables have rejected the null hypothesis and accepted the alternate hypothesis. That is, there exists a statistically significant difference in inequality of means in all the above-mentioned parameters. Hence to study the equality of survival curves of different variables, the Kaplan -Meier (KM) method to estimate overall survival (OS) time is used for the analysis, and the results are below (Figure 1).

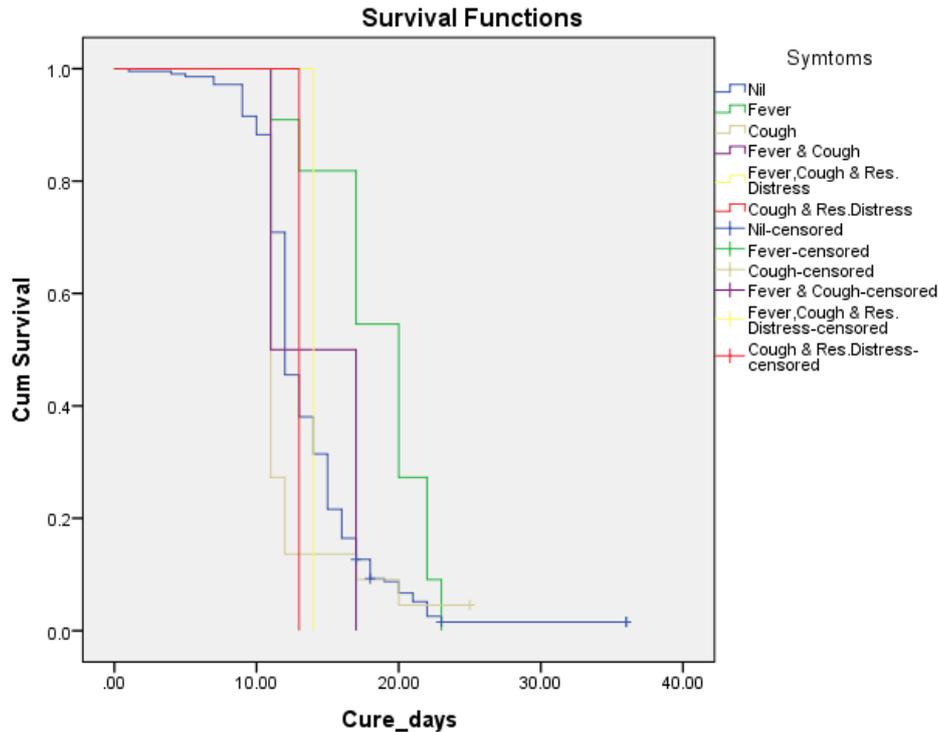


Figure1: Survival Curve of Symptoms

All positive cases became negative and discharged from the hospital are considered the events else considered censored. Out of the 251, 6 cases are censored, and 245 are events. Since the p-value of the calculated chi-square test is <0.05 , reject the null hypothesis that all the compared curves are the same (Figure1). From the above chart, it is clear that all patients with Fever & Cough, Cough, Fever, and Cough & Respiratory Distress are discharged from the hospital during the study period. But patients had a fever and no symptom group; not all patients were discharged during the study period and considered censored.

In 90.9% of patients with fever recovered later - 11 days. 91.5% of patients without symptom have a length of stay in hospital is greater than 9 days. 27.3% of patients with cough take more than 11 days in a hospital. All 251 cases were cured of Coronavirus infection, but 6 cases were not discharged on the data collection's closing day.

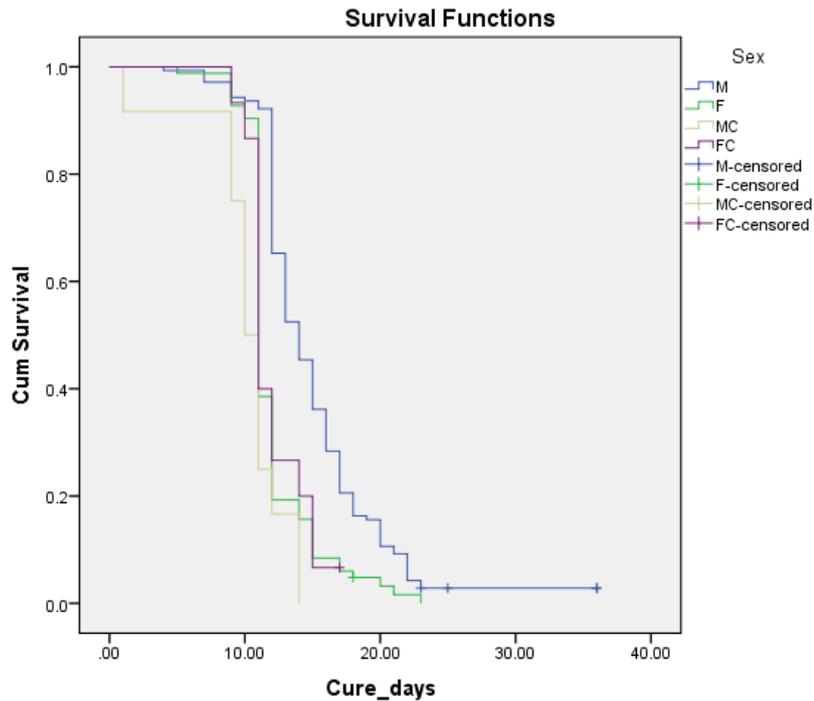


Figure2: Survival Curve of Gender

There was a significant difference in the survival curves of male(M), male child(MC), female(F), and female child(FC) patients. (Log-rank statistic =59.417, df =3, $p < 0.001^{**}$). In 92.2% of Male patients are take greater than 11 days for recovery from Coronavirus infection, and 4 male patients were not discharged from the hospital till the last day of the survey. 92.8% of Female patients have a length of stay in hospital is greater than 9 days, and one female was not discharged from the hospital till the last day of the survey. 75% of Male Child patients take more than 9 days in the hospital, and all MC are discharged from hospital. 86.7% of Female Child patients take more than 10 days in the hospital, and one FC was not discharged from the hospital till the last day of the survey(Figure2).

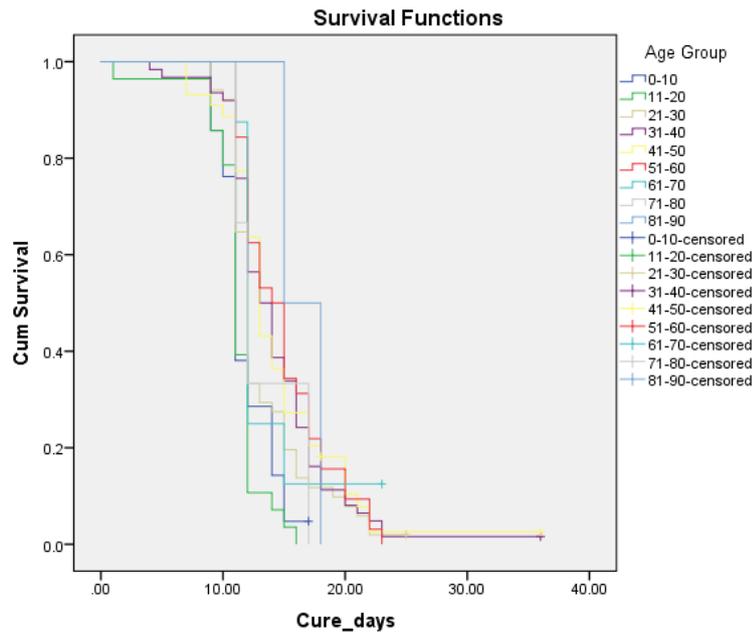


Figure3: Survival Curve of Age Group

There was a significant difference in the survival curves of different age groups of patients. (Log-rank statistic =35.716, df =8, $p < 0.001^{**}$). For the age group, 0-10 length of stay varies from 9 to 17 days, 76.2% of cases LS was greater than 10 days with one censored case. In the age group 11-20, LS varies from 1 to 16 days, and 85.7% of cases LS is greater than 9 days with zero censored case. For the age group 21-30, LS varies from 9 to 25 days, and 92.2% have LS greater than 10 days with one censored case. In the category 31-40, LS varied from 4 to 36 days, and in 91.9% of the cases, LS greater than 10 days with one censored case. In the next group, 41-50 LS varies from 7 to 36 days, and for 88.6% of cases LS greater than 10 days with one censored case. For the next group, 51-60 LS was from 11 to 23 days, and for 84.4% of the cases LS greater than 11 days with complete discharges. The 61-70 group LS varies from 11 to 23 days, and for 87.5% of the cases, LS greater than 11 days with one censored case. 71-80 group LS varies from 11 to 17 days, and 66.7% of cases LS more than 11 days with all discharges. For the last group, 81-90 LS was 15 and 18 days, with all cases discharged (Figure3).

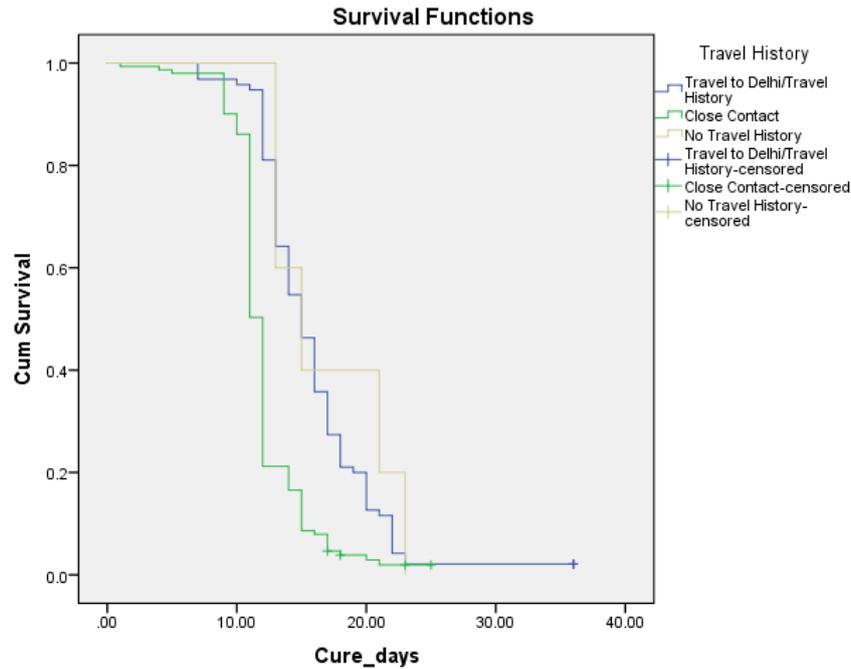


Figure4: Survival Curve of Travel History

There was a significant difference in the survival curves of the different travel histories of patients. (Log-rank statistic =54.679, df =2, p= <0.001**) (Figure4).

Patients with travel history have a length of stay varies from 7 to 36 days, 94.7% of patients have LS greater than 11 days, with 2 censored patients in the group. Patients having close contact have LS varies from 1 to 25 days; 90.1% of patients take more than 9 days of LS in the hospital with 4 censored patients in this group. Patients have no travel history LS varied from 13 to 23 days, and 60% of patients in this group takes more than 13 days of LS in the hospital with all discharges.

Table 3. Descriptive Statistics of Survival Data (SPSS Output of Kaplan-Meier Estimator)							
Variables	Mean Survival Time (Days)	95% CI	Median Survival Time	95% CI	Log Rank	Df	Sig
Symptoms							
Nil	13.58	12.98-14.18	12.000	11.59-12.41	11.498	5	0.042
Fever	18.36	16.11-20.61	20.000	16.62-23.39			
Cough	12.46	10.99-13.92	11.000				
Fever & Cough	14.00	8.12-19.880	11.000				

Fever, Cough & Res.Distress	14.00	14.00-14.00	14.000				
Cough & Res.Distress	13.00	13.00-13.00	13.000				
Overall	13.74	13.17-14.31	12.000	11.59-12.41			
Gender							
M	15.14	14.31-15.96	14.000	13.15-14.85	59.417	3	<0.001**
F	12.10	11.49-12.71	11.000	10.79-11.20			
MC	10.17	8.29-12.05	10.000	8.87-11.13			
FC	12.07	10.99-13.14	11.000	10.47-11.53			
Overall	13.74	13.17-14.31	12.000	11.59-12.41			
Age Group							
0-10	11.81	10.89-12.73	11.00	10.42-11.58	34.823	8	<0.001**
11-20	11.07	10.14-12.01	11.00	10.54-11.46			
21-30	13.27	12.30-14.25	12.00	11.59-12.41			
31-40	14.29	13.14-15.45	13.00	11.60-14.40			
41-50	14.52	12.97-16.07	13.00	12.28-13.72			
51-60	14.91	13.66-16.15	14.00	12.15-15.85			
61-70	13.63	11.06-16.19	12.00	11.52-12.48			
71-80	13.33	9.69-16.97	12.00	10.40-13.60			
81-90	16.50	13.56-19.44	15.00				
Overall	13.74	13.17-14.31	12.00	11.59-12.41			
Travel History							
Travel to Delhi/Travel History	15.87	14.94-16.80	15.00	13.94-16.06	54.679	2	<0.001**
Close Contact	12.14	11.64-	12.00	11.80-			

		12.63		12.20			
No Travel History	17.00	12.89-21.11	15.00	10.71-19.29			
Overall	13.74	13.17-14.31	12.00	11.59-12.41			

Patients without symptoms have, on average, takes 13.58 days (CI 12.98-14.18) of hospital stay. Patients having fever have 18.36 days (CI 16.11-20.61) is the length of hospital stay. Similarly, patients with cough have 12.45 days(CI 10.99-13.92), Fever & Cough takes 14 days(CI 8.12-19.88), Fever, Cough & Res. Distress had 14 days, Cough & Res. Distress takes 13 days is the average length of stay in hospital to discharge after having COVID 19.

Male patients' average length of stay is 15.14 days (CI 14.31-15.96) median LS was 14days. For females, the average LS was 12.1 days (CI 11.49-12.71) median LS was 11 days. In MC, the average LS was 10.17 days(CI 8.29-12.05), median LS 10 days, and FC average LS was 12.07 days (CI 10.99-13.14) with median LS 11 days.

Age Group 0-10 has average LS 11.81 days (CI 10.89-12.73) median LS 11 days. 11-20 age group have average LS 11.07 days (CI 10.14-12.01) median LS 11 days. Age group 81-90 was the highest average LS of 16.50 days (CI 13.56-19.44) with median 15 days; the second highest average LS was for the age group 51-60 with 14.91 days (CI 13.66-16.15) with median 14 days. The third highest average LS is for the category 41-50, 14.52 days(CI 12.97-16.07) days with a median of 13 days.

Patients with travel history have average LS 15.87 days (CI 14.94-16.80) median LS 15 days. Close contact has an average LS of 12.14 days (CI 11.64-12.63) median LS 12 days. No travel history group has average LS 17 days (CI 12.89-21.11) median LS 15 days. On average, we have 13.74 days (CI 13.17-14.31) was the average length of stay for the patients taking ZVcKK need to stay in hospital after having infected by Corona Virus (Table 3).

4. DISCUSSION

The dataset of patients indicates almost all the primary contacts who had a travel history are the source of infection. Invariably all the sexes including children were affected. The length of the stay of asymptomatic patients is lesser than that of the patients who are symptomatic. Among the symptoms cough, fever, and respiratory distress were reported. Even though there is a good reduction in the viral infection some patients reported ground glass opacity (GGO) of the lung which describes the long-term complication of the disease. 85-year-old women has been referred to a higher centre due to this GGO. Except this case among the 251 all the other 244 cases have been discharged and 6 patients were under treatment, none of the cases required ventilators or oxygen support. Age has an influence over the LS. Higher the age group longer the LS. Patients with primary contact travel history had an influence on LS, however the average LS among all the cases have been reported as 13.5days. Integrative therapy has its own benefit which is reflected in reduction of LS.

5. CONCLUSION:

The overall median length of stay was 12 days for those who are taking ZVcKK (Median ST CI- 11.59-12.41), and the average length of stay was 13.74 days (CI 13.17-14.31) for those having to take ZVcKK.

The result of a similar study on pneumonia patients in Wuhan shows that the median length of stay for all confirmed inpatients was 19 days [4]. On comparing with this result, patients taking ZVcKK have a saving of 7 days. i.e., the speed of relief is higher while using ZVcKK in an integrative manner.

6. STRENGTH AND LIMITATIONS OF THE STUDY

- The last admission day was 26th April 2020, and discharges were taken for analysis up-to 5th May 2020, so for the last admission, only 10 days for observation.
- Only 15.1% of them have collected with symptoms and need to concentrate on data collection. Headache, Loss of taste or smell, Rigor with chills, Sore throat, Shortness of breath, Muscle pain symptoms were not documented/reported.
- No reports from other studies in India regarding the Length of hospital stay of Covid 19 patients are available, and hence no comparison can be made with the Indian Scenario. This study could be widened by collecting a large volume of data from different Streams / Different Interventions used to compare.

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