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Forecast Model of Dengue and Co-infection with Typhoid using Clinical Parameters

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Abstract

Dengue and co-infection with typhoid infection is increasingly recognized as one of the world's emerging infectious diseases. We have appraised Complete Blood Count (CBC) parameters and serological NS_1, IgG/IgM rapid test data along with survey questionnaire of 314 suspected dengue and typhoid patients with Acute Febrile Illness (AFI) symptoms patients from the different villages of Sonepat district, Haryana to predict dengue and co-infection with typhoid model. Among those suspected patients, 50 dengue positive (14 primaries and 37 secondary infections) in age groups 10-39 years, 86 typhoid positive (64 primaries and 22 secondary infections) in age groups 10-49 years, 8 co-infection cases in age groups 10-29 year and 40-49 years mostly were reported respectively. As per bayesian analysis model and logistic regression model, TLC<4000 cells/cmm (leukopenia) of dengue, MCH>32 pg of typhoid and MCV<83 fL of co-infection was mostly statistically significant ($p<0.05$) among different clinical parameters with high ROC value (area ± SE) with 61-71% accuracy of disease diagnosis evaluation. We identified important CBC parameters to qualify the distinction of dengue, typhoid and co-infection patients with AFI and for more confirmation, a further investigation should be designed for early diagnosis and treatment for the patients.

Keywords: Dengue • Typhoid • Co-infection • CBC• Statistical data analysis • Predictive model

Introduction

AFI is a common clinical syndrome among patients seeking hospital care in India. It is seen in both grown person and youngsters during the monsoon with highest number of vector and water-borne diseases like co-infections of dengue with typhoid, malaria, chikungunya and other bacterial or viral diseases in endemic areas [1]. The signs of dengue may imitator other illnesses such as leptospirosis, influenza, Salmonella typhi, Japanese encephalitis, chikungunya and malaria [2]. In the year 2019 alone, India had reported 55,217 cases and 370 deaths from dengue. Similarly typhoid infection is also vital cause of morbidity and mortality worldwide. Over 22 million new typhoid cases were reported each year in the biosphere resulting in 200,000 deaths. In the year 2019, 1.06 million cases and 346 deaths from typhoid fever were reported in India. Co-infections of dengue with typhoid having overlapping symptoms have been reported only in New Delhi and South India which makes the clinical diagnosis difficult [3]. In India, dengue fever is mostly credited to all febrile infections during the rainy season period (September to November) if established through laboratory analysis. It is a communal practice for patients with temperature to appointment a health care capacity only if fever persists next 2-3 days of unambiguous self-medication. If dengue and typhoid fever are not advanced appropriate, may prime to life frightening significances. Dengue and co-infection with malaria and further arboviral diseases has been deliberated in many parts of the world [4]. Epidemiology of infectious diseases have been considered and testified in India and abroad. However, there is insufficiency of data regarding dengue and typhoid co-infection in both, the industrialized and the emerging world. Coexisting dengue and typhoid fever has been described hardly in the literature [5]. Therefore, these study efforts to find the present co-infection rates in Delhi-NCR, Sonepat areas.

Materials and Methods

Study area and data collection

A surveying data analysis was done total 314 patients in PR Institute of Medical Science and Research (PRIMSR) hospital in Delhi-NCR, Sonepat. Individual patients' data from different villages of Sonepat district, Haryana which is under Delhi-NCR (28.9268° N, 77.0967° E) were collected with acute febrile phase of illness (less than 12 days) from the pathology laboratory of PRIMSR, SRM University, Delhi-NCR, Sonepat and Centre for Drug Design Discovery and Development (C4D). All the suspected patients' data

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were reviewed for demographic, clinical, laboratory and outcome data. The descriptive data analysis has been done on gender, age, place and different symptomatic and clinical parameters of AFI patients with questionnaire form fill-up.

Hematology and serology analysis

The finding of dengue, typhoid and co-infection (primary & secondary) is carried out on the basis of clinical, epidemiological and laboratory data from other acute febrile phase of less than 12 days illness. The CBC parameters such as Hemoglobin (Hgb), Total Leukocytes Count (TLC), Erythrocyte Sedimentation Rate (ESR), PCV: Haematocrit/Packed Cell Volume (PCV), Red Blood Corpuscles (RBC), Platelets (PLT), Mean Corpuscular Volume (MCV), Mean Cell Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Neutrophils, Lymphocytes, Eosinophils and Monocytes were analyzed. Serological data were analysed depend on specific Dengue Day 1 Test-NS1, IgG/IgM ((J. Mitra and Co. Pvt. Ltd) and specific Typhoid Rapid Test-IgG/IgM (CTK Biotech Inc) result which were used to detect dengue and typhoid infection at the pathology laboratory of PRIMSR.

Statistical analysis

The collected data from patients was analyzed using SPSS statistical software (version 20) which is further represented as descriptive clinical data analysis; logistic regression and Receiver Operating Characteristic (ROC) analysis model with P value ($p<0.05$; statistically significant); Bayesian analysis model for disease diagnosis evaluation to predict prevalence of disease (POD), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of test [6-8].

Results

Descriptive data analysis

Among AFI patients, 314 were confirmed with 14 primary and 37 secondary dengue infection; 64 primaries and 22 secondary typhoid infection of maximum number male patients in the age group of 10-30 year. From the sample of one year, it was found that male are highly infected with dengue virus than female; patients from age group 10-19 years and 20-29 years were most affected by dengue, typhoid and co-infection also.

The dengue cases were highly reported from places that are Badhkhalsa, Jakholi, Sewli, and Rai; typhoid cases were reported from Aterna, Badhkhalsa, Nangalkalan, Jakholi, Patla, Piao, Sewli, SRM, Rasoi villages and co-infection were reported from Badhkhalsa, Nangal kalan, Patla, SRM villages nearby Delhi-NCR, Sonepat area. 102°F-104.9°F temperature was found in dengue and typhoid infection patients, but in co-infection patient temperature was measured as 102°F-103.9°F.

In our study, symptomatic measurement had been done on joint pain, muscular pain, headache, eye pain, nausea/vomiting, cough, rash, diarrhea and abdominal pain where maximum number of positive dengue positive patients were having joint pain, muscular pain, eye pain, nausea/vomiting, cough and rash; typhoid positive patients were having joint pain, diarrhea and abdominal pain with statistically significant value ($p<0.05$) using logistic regression validation. But there was no significant value for symptoms of co-infection. Also in our study we revealed that 48 dengue positive patients were having 1-4 days fever, 44 typhoid positive patients were having 8-15 days fever and co-infection patients were having 1-7 days fever.

There is no medicine available for dengue and co-infection with typhoid. In our present study, the patient data reveals that among 314 acute febrile patients, 20 were dengue positive, 86 typhoid positive and 6 co-infection patients were treated with antibiotics; 44 dengue positive, 30 typhoid positive and 4 co-infection patients treated with painkiller medicines; 50 dengue positive, 86 typhoid positive and 8 co-infection patients treated with paracetamol; 6 dengue positive, 4 typhoid positive and 1 co-infection patients were treated with herbal medicines; 29 dengue positive, 17 typhoid positive, 3 co-infection patients were treated with home remedies.

Hematological data analysis

Basis of hematological data analysis, our findings showed that maximum number of patients were dengue positive in normal range of Hgb in male, neutrophils, lymphocytes, eosinophils, monocytes, PCV in male, MCV, MCH, MCHC, but in abnormal range of TLC, ESR in male, RBC in male, platelets. Also there was maximum number of typhoid and co-infection positive patients in normal range of Hgb, TLC, neutrophils, lymphocytes, eosinophils, monocytes, PCV, platelets, MCV, MCH, MCHC, but in abnormal range of ESR in male and female, RBC in male respectively.

Serological data analysis

In our study, we analyzed the primary and secondary infection of dengue (NS_1-Negative; IgG-Negative; IgM-Positive, NS_1-Positive; IgG/IgM-Negative, NS1-Positive; IgG-Negative; IgM-Positive, NS_1-Negative; IgG-Positive; IgM-Negative, NS_1-Negative; IgG/IgM-Positive, NS_1-Positive; IgG/IgM-Positive, NS_1-Positive; IgG-Positive; IgM-Negative) and typhoid (IgG- Negative; IgM-Positive, IgG-Positive; IgM-Negative, IgG/IgM-Positive) of positive dengue, typhoid patients. Among the all patients, there were 14 primary, 37 secondary dengue infections and 64 primary, 22 secondary typhoid infections.

Sensitivity and specificity analysis

In our present study, we analyzed clinical data to test predictive model with sensitivity, specificity, prevalence of disease, diagnosis evaluation accuracy rate. Using Bayesian analysis model, dengue diagnosis evaluation determined 63.24% accuracy rate in TLC<4000 cells/cmm (41.03% sensitivity and 93.10% specificity with 57.35%POD) and also typhoid diagnosis evaluation determined 58.32%accuracy rate in Hgb<12 gm/dL (Female) (39.37% sensitivity and 60.43% specificity with 50.23% POD), 55.34% accuracy in RBC<4.2 cells/cmm (Female) (19.57% sensitivity and 57.39% specificity with 18.14% prevalence of disease), 62.87% accuracy in MCH>32 pg (22.18% sensitivity and 63.31% specificity with 27.75% POD; to predict co-infection diagnosis evaluation determined 61.16%accuracy in Hgb<13 gm/dL (Male) (0.00% sensitivity and 50.98%specificity with 22.92% prevalence of disease, 54.23% accuracy in MCV<83 fL (15.55% sensitivity and 50.35% specificity with 52.65%POD).

Logistic regression analysis

The data of dengue, typhoid and co-infection has been analyzed to develop predictive model using logistic regression, where TLC in dengue; in typhoid Hgb, RBC and MCH in typhoid; Hgb, MCV in co-infection were found statistically significant ($p<0.05$) with good likelihood model ratio and chi-square value of clinical data parameters.

ROC analysis

In our analysis ROC analysis was done with best logistic regression results to compare the useful parameters of test TLC (cells/mcL) in dengue model, MCH (pg) in typhoid model and MCV (fL) in co-infection model obtaining an area under the curve of 0.68 ± 0.07; 0.57 ± 0.03 and 0.79 ± 0.12 respectively which were statistically significant ($p<0.05$).

Discussion

AFI is a communal cause of patients suffering in India. Now a days, dengue, typhoid and co-infection are major health problem which can't differentiate symptoms from AFI symptoms and develops a diagnostic challenge for the clinicians. Typhoid and viral illnesses like hepatitis, influenza, chikungunya etc are very similar symptomatic co-infection disease in dengue patients. But Seshan, et al. (2016) revealed that during dengue season, maximum number of co-infection patients was infected in India due to S. typhi which is responsible for typhoid disease. ELISA test for dengue and widal test for S. typhi infection was conducted by widal test in Delhi hospital [9].

Many scientists reported the different opinion on dengue, typhoid and co-infection case report duration. Because every year the time duration of dengue, typhoid cases was changed. In India, dengue virus causes epidemic from August to November, during the humid season. A part from the various study, Srinivasaraghavan, et al. and Bhan, et al. reported that Dengue and typhoid fever is occurred in Delhi and all over India during the rainy season (July- October) [10, 11]. But there was no report on case season in Delhi-NCR, Sonepat areas. In our present study, we have shown that all the AFI patients with dengue, typhoid and co-infection were reported from September to December in Delhi-NCR, Sonepat, Haryana areas. Co-infections with common endemic pathogens can prove to be a diagnostic challenge especially during dengue outbreaks. This study would be helpful for the disease awareness and prevention in the different parts of rural India.

In previous research, Rasuki, et al. reported that headache, joint leg pains, arthralgia, myalgias may attend [12]. Gomez, et al. revealed that in typhoid fever, continuous frontal headache, mild arthralgia, multiple joints pain, back pain may occur and also stated that constipation is more mutual than diarrhea for typhoid patients [13]. Gubler, et al. reported that in dengue fever, constipation, diarrhea and respiratory indications are frequently described and may be due to simultaneous infections [14]. Bansal, et al. reported that dengue and co-infection with typhoid positive case was found in 32-36 year old women with 4 days fever with chills, body ache, and abdominal discomfort and anorexia symptoms [15]. In our study, we observed that fever, headache, muscular pain and diarrhea were common in dengue, typhoid and co-infection patients. This symptom based report will be help to develop new medicine for dengue, typhoid and co-infection depend on common symptoms.

There are various tests available for the diagnosis of dengue and typhoid disease but there is no diagnosis available for co-infection. Parry, et al. suggested that initially suspected patients would be tested with NS_1, IgG/IgM day 1 test for dengue [16]. Baba, et al. reported that widal rapid serological S. typhi with IgM and/IgG test was useful for suspected typhoid patients as early as 4-5 days of fever [17]. Agrawal, et al. reported that Dengue NS1, IgG/IgM and rapid S. typhi IgM test were used for detection of dengue, co-infection with in New Delhi areas [18]. Seshan, et al., reported that a dengue IgM test was suggested on 8 days fever to diagnosis co-infection. In our study we used NS_1, IgG/IgM day 1 test (J. Mitra and Co. Pvt. Ltd.) for dengue and typhoid IgG/IgM rapid test (CTK Biotech Inc.) for suspected S. typhi patients.

As per previous study, Ochiai, et al. stated that 5 year and 15 year age group people were reported outstanding to typhoid fever [19]. Co-infections of dengue and typhoid have been detected in large case sequence of febrile kids. Though co-infections of dengue and typhoid have been testified in few mature patients, there was very insufficient information in patients till date in India. Sharma, et al. reported that among 659 suspected patients 141 tested positive for dengue and 11 was co-infection with typhoid. The maximum number of positive cases seen in age group 10-30 years in dengue and co-infection with typhoid patients and also stated that female patients were more infected than male patients [20]. Agrawal, et al. reported that 251 positive dengue patients, 9 were co-infection with typhoid positive detected in New Delhi areas. Maximum dengue positive cases were found in age group 20-40 years. In our study, we observed that the patients from age group 10-19 years and 20-29 years were most affected by dengue, typhoid and co-infection. Also our study revealed that maximum number of positive dengue, typhoid and co-infection cases were reported in male than female.

No research was reported on demographic representation of primary, secondary infection and remedies for dengue and typhoid positive patients. Because there are no medicines available till now. As per doctors prescribed suggestions from PRIMSR hospital in Delhi-NCR, Sonepat, we revealed that paracetamol and pain killer medicine could be used for the preliminary treatment of dengue, typhoid and co-infection. Furthermore, among the patients, 14 dengue, 64 typhoid primary infections and 37 dengue, 22 typhoid secondary infections were reported.

Srinivasaraghavan, et al. stated that a case of co-infection of typhoid fever with dengue fever in 10 years old teenager in India found in PCV (40%), PLT (21000/cu.mm) and leukopenia (4200/cu.mm) and neutrophils (85%). Also, Bansal, et al. reported that two middle aged woman was found dengue, co-infection with typhoid with significant value of thrombocytopenia (91,00-110,000/mm^3) which was a low platelet count. Moreover, Seshan, et al. reported that a case of 24-40 years old male presented significant decrease value in PLT (90 x 10^9-120 x 10^9/μL) and TLC (3800/mm^3) with headache, myalgia, nausea in South India. No researcher has conveyed on predictive model for further investigation to conformation of early diagnosis and treatment for the patients. In our present study, as per bayesian analysis model and logistic regression model, TLC<4000 cells/cmm (leukopenia) was mostly statistically significant ($p<0.05$) among

different clinical parameters with high ROC value (area ± SE) through 35-58% POD, 41-100% sensitivity, 38-94% specificity with 62-71% accuracy of dengue disease; MCH>32 pg among different clinical parameters with high ROC value (area ± SE) through 27.75% POD, 22.18% sensitivity, 63.31% specificity with 62.87% accuracy of typhoid disease was statistically significant ($p<0.05$); MCV<83 fL was mostly statistically significant ($p<0.05$) among different clinical parameters with high ROC value (area ± SE) through 52.65% POD, 15.55% sensitivity, 50.35% specificity with 54.23% accuracy of co-infection disease. The significant clinical performances and useful CBC parameters to enable the differentiation of dengue, typhoid and co-infection patients with AFI were identified.

Conclusion

The present study reported the occurrence of dengue and co-infection with typhoid in Delhi-NCR, Sonepat area which are important for Haryana state. Our patient had a dengue and co-infection with typhoid in middle young age group male. Paracetamol and pain killer medicines could be used during dengue and co-infection with typhoid infection with the guidance of doctors. The proposed predictive models are simple, easily available, and cost effective and may identify useful clinical parameters to differentiate between dengue, typhoid and co-infection and other acute febrile illness diseases in rural hospitals of high transmission endemic areas. In our research, Fever, headache, muscular pain and diarrhea were the most common symptoms and finding in the dengue and co-infection with typhoid cases. Hematological findings including TLC, MCH and MCV changes were observed in dengue, typhoid and co-infection positive cases respectively. The proposed models can be a valuable primarily screen tool for dengue and co-infection with typhoid patients' during epidemic periods in high transmission rural areas and to help reduce the morbidity and mortality of infection for further diagnosis and treatment. This is the first study from Delhi-NCR, Sonepat to report the dengue and co-infection with dengue fever.

Conflict of interests

We declare that we have no conflict of interests.

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Ethical Considerations and Consent

Protection of human and animal subjects. The authors declare that no experiments were performed on blood sample of humans or animals for this study. We have collected data from PR Institute of Medical Science and Research Hospital. All authors declare that written informed consent was obtained from the patient for publication of this paper.

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