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A retrospective study: distributions of hematological parameters and co-morbidities with acute febrile illness in India

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Abstract

Background: Acute febrile illness is a non-specific term used differently in clinical and public health contexts. Research on the etiology of Acute febrile illness is important in directing appropriate empiric treatment and case management, prioritizing resources, developing prevention and control measures, identifying novel pathogens and outbreaks, and supporting global health security goals.

Methods: During 2019-2020, physicians screened patients of 1 year in outpatient departments in private hospitals. Patients with high fever were randomly enrolled in Yatharth hospital, Gautam Buddha Nagar, Greater Noida, Uttar Pradesh, India during assessment with onset within past 14 days.

Results: This study involved 175 hospitalized patients with fever, with a median age of 39 years and 58% males. The majority of cases were undifferentiated, with only 30.2% having a specific cause for the fever such as enteric fever or viral fever. Respiratory tract infection was the most common non-malarial AFI, followed by urinary transmitted infection. Patients aged 31-45 years made up the highest percentage of cases.

Conclusions: Different age groups showed trends in laboratory parameters, including mean hemoglobin values and mean PCV count. Patients with underlying comorbidities showed deviations in lab investigations, with diabetes and CAD having elevated GGTP, SGOT & SGPT levels, and CKD and COPD having greater mean RDW (%) values. Tuberculosis and CKD were associated with anemia. Tuberculosis and CKD were associated with anemia.

Keywords: Acute febrile illness, Urinary transmitted infection, anemia, tuberculosis, non-malarial

Background

Rural areas in low- and middle-income countries in South and Southeast Asia are among the most underprivileged have an unclear picture of their health problems(2). Infectious diseases, especially febrile illness, continue to be a major cause of morbidity and mortality in these areas(22, 5, 27). Acute febrile illness (AFI) is responsible for 1.9 million deaths annually in India (4,23).Acute febrile illness (AFI) is a non-specific term used differently in clinical and public health contexts(19). Research on the etiology of AFI is important in directing appropriate empiric treatment and case management, prioritizing resources, developing prevention and control measures, identifying novel pathogens, outbreaks and supporting global health security goals(12). An observational cohort study was conducted to characterize various indicators associated with AFI and other concomitant conditions/diseases through blood profiling (8). Acute febrile illness (AFI) is a clinical syndrome characterized by fever and other non-specific symptoms(7), the underlying cause of AFI can vary widely and can be caused by viruses (26) and bacteria (6). Non-malarial febrile illnesses (NMFI) are infectious diseases that cause fever but test negative for malaria (6; 27). Diagnostic AFI refers to infectious diseases that are able to be diagnosed through laboratory testing, such as enteric fever (16, 11), influenza, scrub typhus (3), *Streptococcal pharyngitis* and dengue (20). Diagnosis of AFI requires a thorough clinical evaluation, while treatment is largely supportive and depends on the underlying cause. Prevention involves measures to reduce the risk of infection and seeking medical attention if symptoms occur. In addition, despite the fact that the etiology of AFI varies significantly depending on the population, geography, and time period. The World Health Organization (WHO) has requested a wide range of etiologic research to pinpoint the microorganisms causing AFI as part of an informal conversation on fever management in peripheral health care settings (29).

The etiology of AFI varies depending on geographic location, age, and immune status of the patient (28). Infection is the most common cause of AFI, with viral infections being the most common etiology (13). Dengue fever, chikungunya fever, Zika virus, and influenza are the most common viral infections causing AFI (18).Bacterial infections such as typhoid fever, leptospirosis, and rickettsia infections are also common causes of AFI. In addition, fungal infections, such as histoplasmosis and coccidioidomycosis, can cause AFI, especially in immunocompromised patients.

The study was conducted retrospectively at Yatharth Hospital in Greater Noida, Uttar Pradesh, India and was an observational patient registry study. Aim of the study to conduct a comparative analysis various hematological parameter in different age groups with specific comorbidities and assess how these variables change in relation to established etiology of AFI.Data were recorded in an excel spreadsheet and summarized using frequency and mean or median.

Methods

Study Design

The entire study was conducted retrospectively at Yatharth Hospital in Greater Noida, Uttar Pradesh, India, and was of the observational [Patient Registry] kind. The first patient's data under evaluation was admitted to the hospital on June 1, 2019, and the last patient's data under evaluation was admitted to the hospital on August 3, 2020.

Ethical Considerations

Prior to the analysis of the patient data, the study proposal was authorized by the Institutional Ethics Committee, Yatharth Hospital. Since all of these cases included admitted patients, where consent has been waived off as this was retrospective study and all data were collected from medical record department. Any data related to patients' identification was not utilized in this study.

Patient Enrollment

Every hospitalized patient's data who reported having a fever and remained in the ward for at least 24 hours was evaluated.175 patients' data in all, including 101 men and 74 women, were under assessment.All ages, including pediatrics, adolescents, adults, and even older adults, were deemed eligible, as were all sexes in the absence of healthy volunteers. Patients who didn't consent were excluded from data analysis. Using digital clinical thermometers, the physician measured the suspected AFI patients' oral and/or axillary temperatures (whichever was possible) and recorded the highest temperature obtained. Eligible patients had a measured fever (oral/axillary temperature ≥100.4˚F).The percentage of enrolled patients affected by each of the etiology of fever disease (bacteria, viruses, fungus and others). Average hospital stays of the febrile patients in connection with the individual etiological factors.

Laboratory Evaluations

The retrieved lab investigations data consist of complete blood count (CBC) (14), liver function tests (LFT) & kidney function tests (KFT). The reports even helped to determine the demographic profile, Comorbidities and different diagnoses of patients on the basis of case to case performed diagnostic tests such as Malaria Parasite Rapid Antigen Test (21), Typhidot etc. with acute febrile illness. Clinically significant outlier determination is based on the pre- specified standardized reference ranges for each biochemistry and hematology investigations.

Statistical Analysis

Data was retrieved from the laboratory reports and subsequently recorded on an excel spreadsheet. Frequency (percentage) was used to summarize categorical values. Continuous variables were summarized as mean and standard deviation (SD) or median and range (when SD was > 50% of mean).

Results

A total of 175 patients'data were recorded and studied during 2019-2020. They were all followed up for the entire duration of the hospital stay. The median age of participants was 39 years, 58% were male, median duration of hospital stay was 3 days. Etiology for fever could be ascertained in 53 patients (30.2%) while 122 remained undifferentiated as 58 cases of non-malarial AFI and rest counted as cases of undiagnosed AFIas shown in Table 1.

Table 1Diagnosed AFI, NMFI and undiagnosed AFI cases distribution with respect to different age groups

Undiagnosed AFI		12	13	14	12	8	5	64
Non-Malarial AFI (58)	**Pneumonitis**	1	1	3	0	3	2	10
	Covid-19	0	1	0	1	0	0	2

	Diagnosed AFI (53									
Age Group	**Malaria**	**Dengue**	**Enteric Fever**	**Viral Fever**	**Influenza**	**UTI**	**RTI**	**Hepatitis C**	**COPD**	**Cholelithiasis**
<15 years	0	1	1	1	1	2	8	0	0	0
16-30 years	1	0	8	3	0	4	5	0	0	0
31-45 years	1	1	9	4	0	1	9	0	0	0
46-60 years	2	1	6	3	1	0	3	0	0	0
61-75 years	0	1	4	1	0	2	4	1	1	0
>76 years	1	0	2	0	0	2	3	0	0	1
Total No. of cases	5	4	30	12	2	11	32	1	1	1

Most common specific diagnosis was found to be enteric fever (typhoid) in 30 patients (17.1%) closely followed by viral fever (n = 12) (6.9%) as shown in figure 1. Of all the NMFI cases, patients predominated with symptoms of respiratory tract infection (RTI) (n =32) followed by UTI cases (n =

11). Maximum number of patients (24%) was in age group 31-45 years, followed by 20.6% in the age group of 16-30 years (Figure 2).

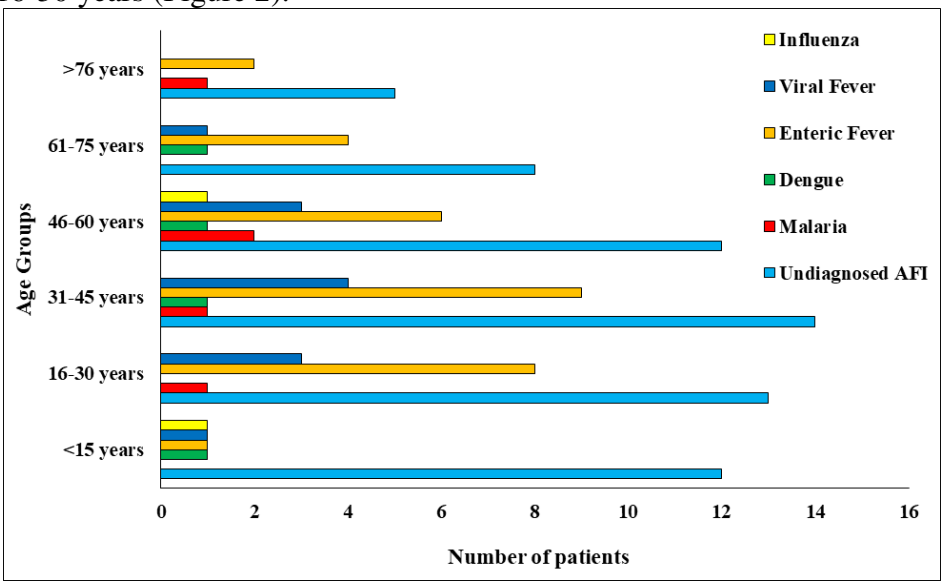

Figure 1Diagnosed AFI and undiagnosed AFI cases distribution with respect to different age groups

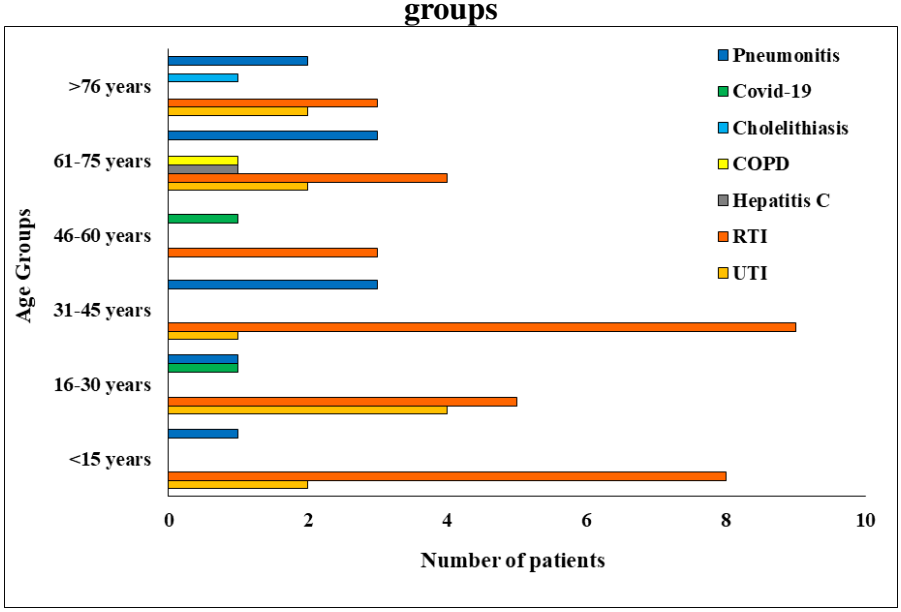

Figure 2Non-malarial febrile illness cases distribution with respect to different age groups

In terms of associated comorbidities, organ-related Inflammation was reported in 16 patients which is 9.1% of the total population followed by cases of diabetes (n = 10). Clinical spectrum of patients shows ageing and dehydration as clinically significant features among the majority of cases marking to 16% and 8% of the population respectively shown in table 2.

Table 2Demographic profile, co morbidities and clinical spectrum of patients with acute febrile illness.

Parameter overall (n=175)		
Gender	Male	101
	Female	74
Age (Years)		39 (31)
Comorbidities	Diabetes	10 (5.71%)
	Hypertension	8 (4.57%)
	Tuberculosis	2 (1.14%)
	Coronary Artery Disease	4 (2.28%)
	Chronic Kidney Disease	4 (2.28%)
	Chronic Liver Disease	1 (0.57%)
	COPD	4 (2.28%)
	Organ related inflammation	16 (9.14%)
Clinical features	Sepsis	5 (2.85%)
	Headache	2 (1.14%)
	Joint pain	1 (0.57%)
	Ageing	28 (16%)
	Dehydration	14 (8%)
	Seizure	1 (0.57%)
	Jaundice	2 (1.14%)
	CVA	2 (1.14%)
	Hypothyroidism	2 (1.14%)
	Abdominal pain	3 (1.71%)

Among all diagnosed febrile illnesses, malaria showed maximum (60%) number of cases with hemoglobin below 12gm/dl and also additionally patients with symptoms of UTI, RTI & Pneumonitis among non- malarial AFI cases showed low hemoglobincount significantly. Out of 50 patients showing leukocytosis, maximum had reported RTI and 08 patients had confirmed diagnosis of enteric fever (typhoid). It was noted that majority (71%) of cases of AFI had normal platelet count i.e., 150000-450000/mm^3. Maximum cases of reduced PCV were of UTI (n = 14), followed by RTI (n = 5). Out of 75 cases who presented reduced PCV, 32 cases were of unspecific fever as shown in table 3.

Table 3: Diagnosed AFI, NMFI, undiagnosed AFI cases distribution with respect to hematological parameters

Undiagnosed AFI (64)	27 (42.1%)	30 (46.8%)	6 (9.37%)	5 (7.8%)	40 (62.5%)	18 (28.1%)	10 (15.6%)	49 (76.5%)	4 (6.25%)	32 (50%)	31 (48.4%)	0 (0%)

Non-malarial AFI population (n=58)						
UTI (11)	**RTI (32)**	**Hepatitis C (1)**	**COPD (1)**	**Cholelithiasis (1)**	**Covid-19 (2)**	**Pneumonitis (10)**
6 (54.5%)	15 (46.8%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	6 (60%)
4 (36.3%)	11 (34.3%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	2 (20%)
0 (0%)	2 (6.25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (20%)
6 (54.5%)	17 (53.1%)	0 (0%)	1 (100%)	0 (0%)	1 (50%)	3 (30%)
4 (36.3%)	11 (34.3%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	5 (50%)
2 (18.1%)	3 (9.3%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	2 (20%)
8 (72.7%)	24 (75%)	0 (0%)	1 (100%)	0 (0%)	1 (50%)	6 (60%)
0 (0%)	2 (6.25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
5 (45.4%)	14 (43.7%)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	5 (50%)
5 (45.4%)	14 (43.7%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	3 (30%)
0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

	Diagnosed AFI population (n=53)				
Parameters	**Malaria (5)**	**Dengue (4)**	**Enteric Fever (30)**	**Viral Fever (12)**	**Influenza (2)**
Low Hemoglobin Count (<12 gm/dL)	3 (60%)	0 (0%)	8 (26.6%)	2 (16.6%)	1 (50%)
Normal Hemoglobin Count (12-15 gm/dL)	1 (20%)	3 (75%)	13 (43.3%)	8 (66.6%)	1 (50%)
High Hemoglobin Count (>15 gm/dL)	1 (20%)	1 (25%)	4 (13.3%)	1 (8.3%)	0 (0%)
Low WBC Count (<4000/mm^3)	0 (0%)	1 (25%)	1 (3.33%)	0 (0%)	1 (50%)
Normal WBC Count (4000-10000/mm^3)	4 (80%)	3 (75%)	17 (56.6%)	9 (75%)	1 (50%)
High WBC Count (>10000/mm^3)	1 (20%)	0 (0%)	8 (26.6%)	2 (16.6%)	0 (0%)
Low Platelet Count (<150000/mm^3)	2 (40%)	1 (25%)	6 (20%)	4 (33.3%)	0 (0%)
Normal Platelet Count (150000-450000/mm^3)	2 (40%)	3 (75%)	20 (66.6%)	8 (66.6%)	2 (100%)
High Platelet Count (>450000/mm^3)	0 (0%)	0 (0%)	1 (3.33%)	0 (0%)	0 (0%)
Low PCV (F<36) (M<40)	2 (40%)	1 (25%)	9 (30%)	3 (25%)	1 (50%)
Normal PCV (F=36-46) (M=40-50)	1 (20%)	2 (50%)	15 (50%)	7 (58%)	1 (50%)
High PCV (F>46) (M>50)	1 (20%)	1 (25%)	0 (0%)	1 (8.3%)	0 (0%)

Findings had revealed age group 31-45yrs to be most dynamic with majorly 14 cases of unspecific fever and 9 cases each of enteric fever (typhoid) & RTI. Mean hemoglobin count (gm/dL) had come out to be normal (12-15gm/dL) for all diagnosed AFI cases with non-significant deviations among the cases with non-malarial AFI and unspecific fever (figure3).

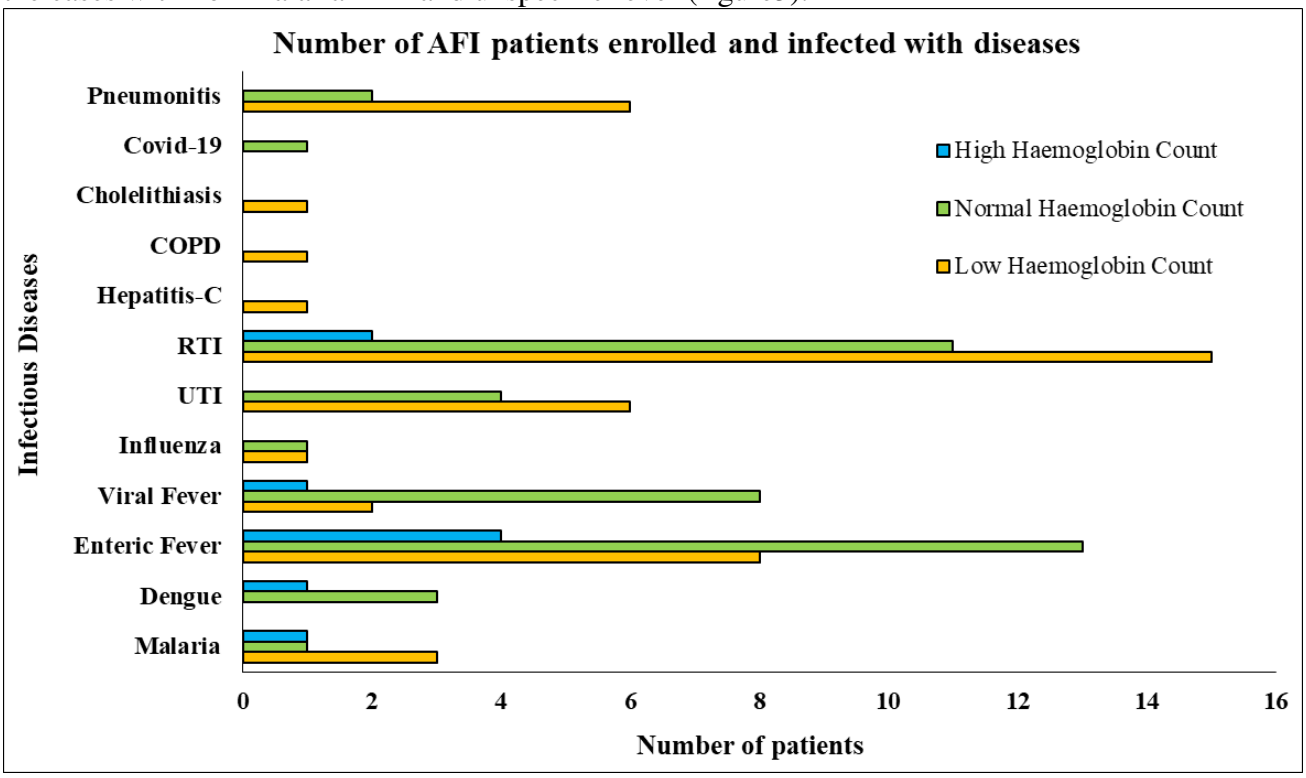

Figure 3Proportionate distribution of infectious diseases over acute febrile illness (AFI) patients significantly showed haemoglobin count.

From the study, it has been observed that non-malarial AFI population (n=58) showed low haemoglobin count (<12gm/dL) followed by diagnosed AFI population (n=53). Total 30 patients showed symptoms of enteric fever, out of which 13 (43.3%) showed normal haemoglobin count (12-15gm/dL) followed by 8 (26.60%) showed low haemoglobin count (<12gm/dL) and 4 (13.30%) showed high haemoglobin count (>15gm/dL).

The differential platelet count between diagnosed AFI and non-malarial AFI are demonstrated in figure 4. Hepatitis C (n=1) and Cholelithiasis (n=1) showed 100% low platelet count (<150000/mm^3). In diagnosed AFI, influenza (n=1) showed 100% normal platelet count (150000-450000/mm^3) followed by dengue (75%), enteric fever and viral fever (66.60%) whereas in NMFI, COPD (n=1) showed 100% normal platelet count followed by RTI (75%), UTI (72.70%), pneumonitis (60%) and Covid-19 (50%) whereas high platelet count (>450000/mm^3) data is negligible.

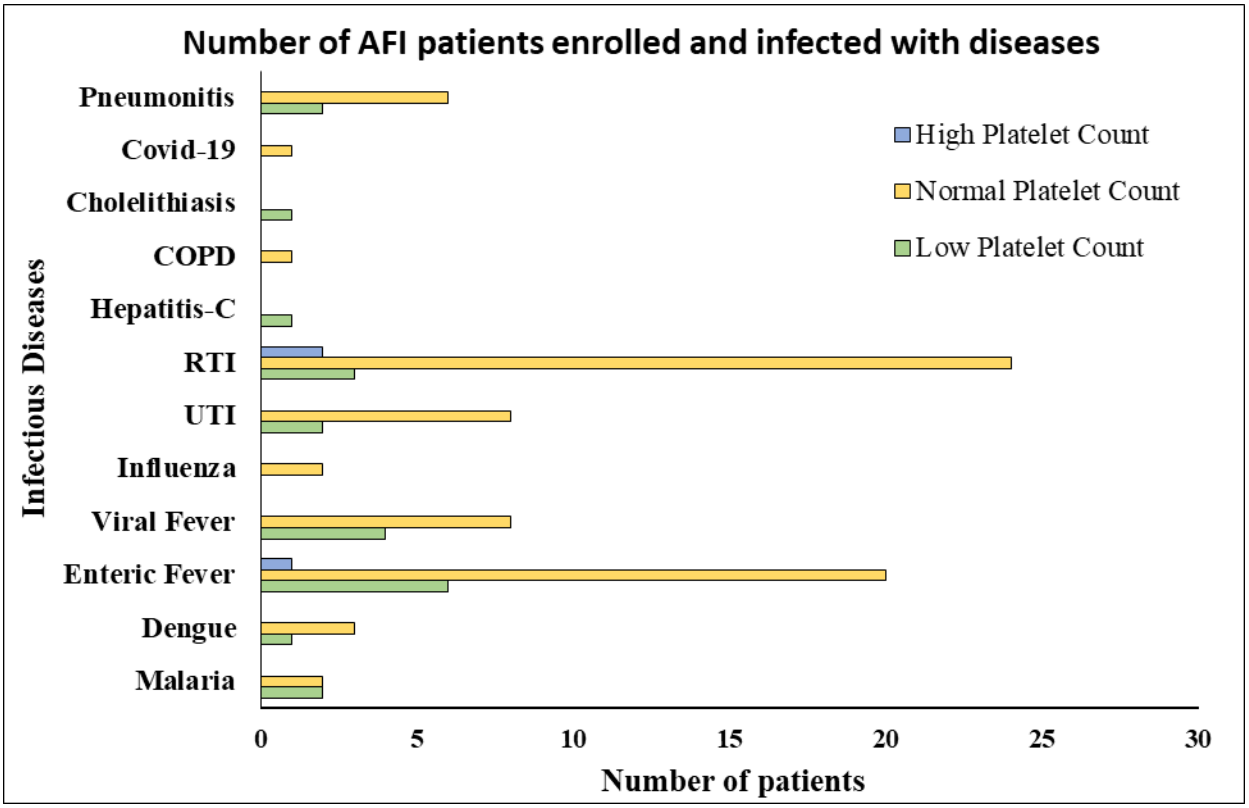

Figure4 Proportionate distribution of infectious diseases over acute febrile illness (AFI) patients significantly showed platelet count.

While the mean values of WBCs (10000/mm^3) have shown non-significant leukocytosis among the cases with RTI & pneumonitis (n=10) and clinically significant elevated count in a case of cholelithiasis 100% low WBC count (<4000/mm^3)was observed in Hepatitis C (n=1), 100% high WBC count (>10000/mm^3)estimated in cholelithiasis (n=1) followed by pneumonitis (50%) (figure 5).

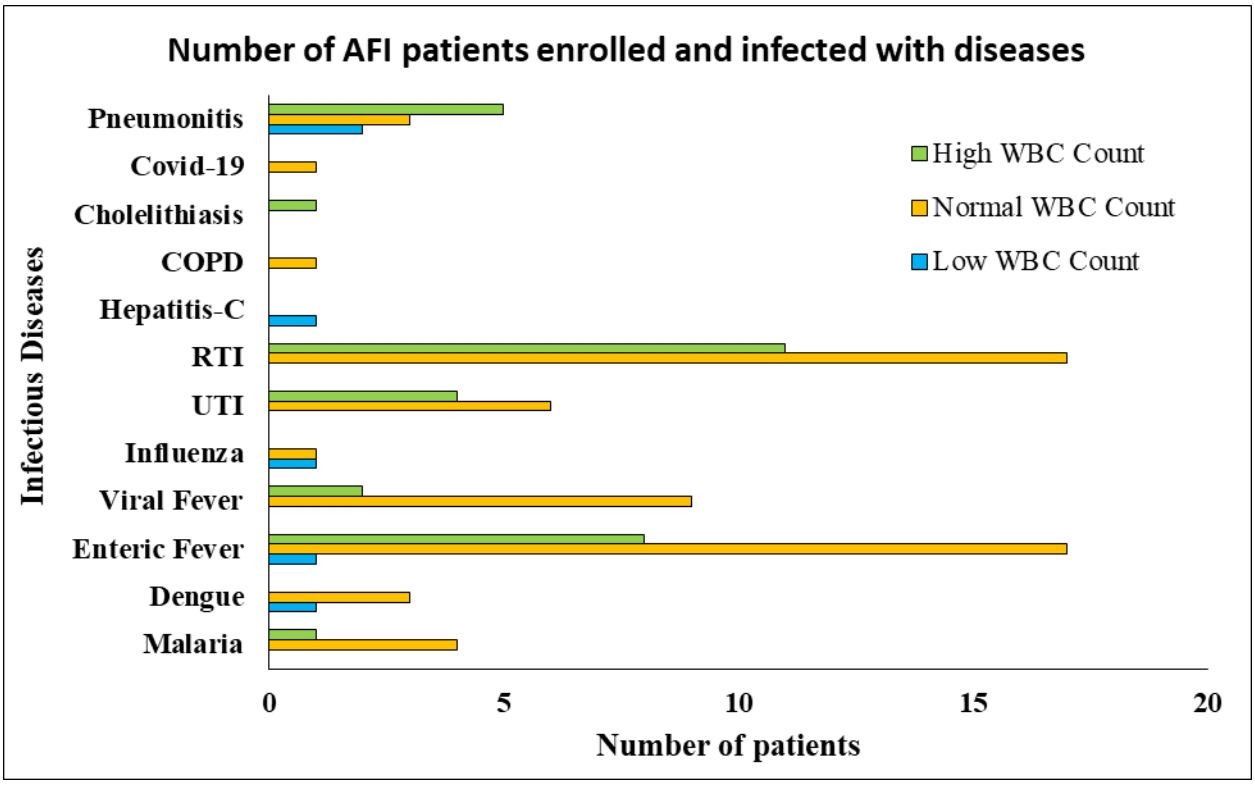

Figure5Proportionate distribution of infectious diseases over acute febrile illness (AFI) patients significantly showed white blood cells count.

Majority of the patients with Illness have shown reduced mean PCV Count, exceptions to the same were cases of dengue and viral fever (Figure6). 100% low PCV count ((F<36) (M<40) observed in hepatitis C (n=1), COPD (n=1) and cholelithiasis (n=1) followed by pneumonitis (50%) and influenza (50%) others are below 50%.

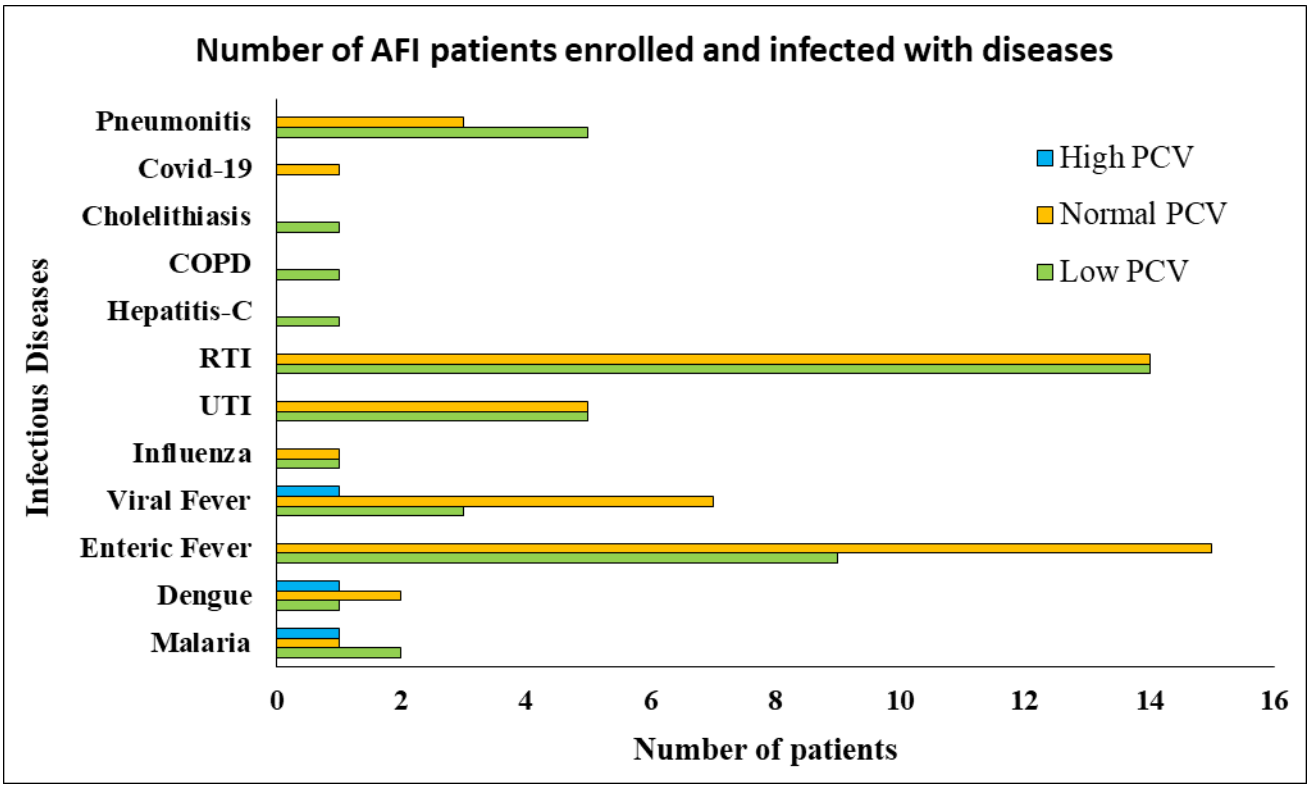

Figure6 Proportionate distribution of infectious diseases over acute febrile illness (AFI) patients significantly showed PCV count.

A condition of thrombocytopenia was observed in a case of Hepatitis-C with a mean value of 0.6 lakhs/mm^3. Exceptionally Elevated Mean C-Reactive Protein Values were observed across all the cases demonstrating significant associated infections leading to comparatively longer duration of hospital stay. In comparison to the other cases among the three classifications, Non-malarial AFI case with Cholelithiasis have revealed clinically significant high mean urea value (mg/dl) i.e., 44.4 mg/dL, followed by cases with Urinary Tract Infection (40.3 mg/dL). High Mean Alkaline Phosphatase Levels along with SGOT and GGTP in blood were noted among the cases of Dengue (n = 4).

AFI population with additional underlying comorbidities such as diabetes, hypertension, tuberculosis, CAD, CKD, COPD &organ-related inflammation proved to be as significant indicators on the basis of deviations in lab investigations. Patients with Diabetes and CAD had exceptionally high Mean GGTP, SGOT & SGPT levels when compared to normal values in other cases. Mean Alkaline Phosphatase levels were found to be elevated in the diabetic cases. COPD followed by CKD population demonstrated greater mean RDW (%) values i.e., 17.2% & 16.1% respectively.

Discussion

Among AFI patients, findings from surveillance shows that most bacterial pathogens such as*Rickettsia*, *Salmonella typhi,*(22)*Salmonella enterica*, and urinary *Escherichiacoli*(9)was observed (16, 24). Dengue was the most frequentlydetected viral infection, predominant in Southeast Asia. Current investigation also identified afew cases of *Leptospira* and one case of Hepatitis C among the enrolled AFI patients.In contrast to many studies focusing on a single pathogen (1, 17),this surveillance tested for multiple pathogens causing acute febrile illness in India (23). Ourfindings extended the work of Robinson et al (2018), where the researchers tested multiple pathogensamong hospital-based febrile patients, both inpatient and outpatient in India

and found most common cause of AFI in adults are vector-borne disease including dengue. Current surveillanceadded value by investigating more samples of AFI focusing on outpatient departments, sampleswere tested irrespective of their presenting sign-symptoms, and study reflect greater risk of exposure of dengue. On the basis of previously studied on AFI in Southeast Asian and in India, higher dengue prevalence risk of 7% in children's and 21% in adults (15, 10). There was extensive seasonal variability in AFI burden and etiology. In the 3 months after the monsoon, vector-borne diseases were found in more than half of adults, driving peak AFI admission. Respiratory infectious diseases were more common in February through April for adults and children, which was the primary driver of seasonal AFI admission variation for children (23).

Conclusion

In conclusion, the study found that a significant proportion of patients with acute febrile illness remained undifferentiated, with only 30.2% having an identifiable cause of fever. Enteric fever (typhoid) and viral fever were the most commonly diagnosed specific illnesses. Respiratory tract infection was the most common symptom among non-malarial AFI cases. The clinical spectrum of patients showed aging and dehydration as significant features, while comorbidities such as organ-related inflammation and diabetes were found to be important indicators for deviations in lab investigations. Laboratory investigations showed characteristics of various underlying comorbidities in patients including diabetes, CKD, COPD and organ-related inflammation.

The study results suggest that malaria is associated with a higher likelihood of low haemoglobin levels compared to other febrile illnesses. Additionally, non-malarial cases of AFI showed a significant association with low haemoglobin levels among patients with symptoms of UTI, RTI and pneumonitis. Leucocytosis was most commonly associated with RTI and enteric fever, while reduced PCV was primarily seen in UTI and RTI cases. Overall, the age group of 31-45 years was found to be the most dynamic, with several cases of unspecific fever, enteric fever (typhoid), and RTI. In conclusion, the analysis of haemoglobin count, WBC count, PCV count, C-reactive protein values, and other factors among diagnosed AFI cases indicates that there are observable differences and significant deviations among the cases. The laboratory parameters show variable trends across different age groups. While some parameters such as mean haemoglobin values and mean PCV count follow a closed parabola, others like mean WBC values exhibit an open parabola. The farthest age groups i.e., those below 15 years of age and above 76 years of age, showed clinically non-significant low values on certain parameters. The study highlights the importance of conducting further research to understand the underlying causes and comorbidities associated with acute febrile illness and developing effective management strategies.

List of abbreviations

AFI: Acute Febrile Illness
CAD: Coronary Artery Disease
CBC: Complete Blood Count
CKD: Chronic Kidney Disease
COPD: Chronic Obstructive Pulmonary Disease
CVA: Cerebrovascular Accident
GGTP: Gamma-glutamyl transpeptidase
KFT: Kidney Function Tests
LFT: Liver Function Tests
NMFI: Non-malarial Febrile Illness
PCV: Packed Cell Volume

RDW: Red cell Distribution Width
RTI: Respiratory Tract Infection
SD: Standard Deviation
SGOT: Serum Glutamic Oxaloacetic Transaminase
SGPT: Serum Glutamic Pyruvic Transaminase
UTI: Urinary Tract Infection
WBC: White Blood Cell
WHO: World Health Organization

Declarations

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References

1. Aalpona FZ, Kamrul-Hasan AB. Study of Bacterial Pathogens in Urinary Tract Infection and their Antimicrobial Sensitivity Pattern in the Setting of Gynecology Outpatient Department. Mymensingh Medical Journal: MMJ. 2020 Oct 1;29(4):838-46.
2. Das P, Rahman MZ, Banu S, Rahman M, Chisti MJ, Chowdhury F, Akhtar Z, Palit A, Martin DW, Anwar MU, Namwase AS. Acute febrile illness among outpatients seeking health care in Bangladeshi hospitals prior to the COVID-19 pandemic. Plos one. 2022 Sep 1;17(9):e0273902.
3. Devasagayam E, Dayanand D, Kundu D, Kamath MS, Kirubakaran R, Varghese GM. The burden of scrub typhus in India: A systematic review. PLoS neglected tropical diseases. 2021 Jul 27;15(7):e0009619.
4. Dhingra N, Jha P, Sharma VP, Cohen AA, Jotkar RM, Rodriguez PS, Bassani DG, Suraweera W, Laxminarayan R, Peto R. Adult and child malaria mortality in India: a nationally representative mortality survey. The Lancet. 2010 Nov 20;376(9754):1768-74.
5. Elven J, Dahal P, Ashley EA, Thomas NV, Shrestha P, Stepniewska K, Crump JA, Newton PN, Bell D, Reyburn H, Hopkins H. Non-malarial febrile illness: a systematic review of published aetiological studies and case reports from Africa, 1980–2015. BMC medicine. 2020 Dec;18:1-7.
6. Escadafal C, Geis S, Siqueira AM, Agnandji ST, Shimelis T, Tadesse BT, Loembé MM, Harris V, Fernandez-Carballo BL, Macé A, Ongarello S. Bacterial versus non-bacterial infections: a methodology to support use-case-driven product development of diagnostics. BMJ Global Health. 2020 Oct 1;5(10):e003141.

7. Gasem MH, Kosasih H, Tjitra E, Alisjahbana B, Karyana M, Lokida D, Neal A, Liang CJ, Aman AT, Arif M, Sudarmono P. An observational prospective cohort study of the epidemiology of hospitalized patients with acute febrile illness in Indonesia. PLoS Neglected Tropical Diseases. 2020 Jan 10;14(1):e0007927.
8. Hemlock C, Luby SP, Saha S, Qamar F, Andrews JR, Saha SK, Tamrakar D, Date K, Longley AT, Garrett DO, Bogoch II. Utilization of blood culture in South Asia for the diagnosis and treatment of febrile illness. Clinical Infectious Diseases. 2020 Nov 1;71(Supplement_3):S266-75
9. Hsu YC, Huang HC, Tang KS, Su LT, Huang YH, Huang HC, Chen IL. Elevated Urinary Hepcidin Level and Hypoferremia in Infants with Febrile Urinary Tract Infection: A Prospective Cohort Study. Children. 2023 May 12;10(5):870.
10. Joshi R, Colford Jr JM, Reingold AL, Kalantri S. Nonmalarial acute undifferentiated fever in a rural hospital in central India: diagnostic uncertainty and overtreatment with antimalarial agents. American Journal of Tropical Medicine and Hygiene. 2008 Mar 1;78(3):393.
11. Khanam F, Darton TC, Ross AG, Zaman K, Pollard AJ, Clemens JD, Qadri F. Case report: Typhoid fever complicated by ileal perforation in an urban slum of Dhaka, Bangladesh. The American Journal of Tropical Medicine and Hygiene. 2021 May;104(5):1755.
12. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, Rudan I, Campbell H, Cibulskis R, Li M, Mathers C. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. The lancet. 2012 Jun 9;379(9832):2151-61.
13. Lorenzi OD, Gregory CJ, Santiago LM, Acosta H, Galarza IE, Hunsperger E, Muñoz J, Bui DM, Oberste MS, Peñaranda S, García-Gubern C. Acute febrile illness surveillance in a tertiary hospital emergency department: comparison of influenza and dengue virus infections. The American journal of tropical medicine and hygiene. 2013 Mar 3;88(3):472.
14. Mave V, Chandanwale A, Kagal A, Khadse S, Kadam D, Bharadwaj R, Dohe V, Robinson ML, Kinikar A, Joshi S, Raichur P. High burden of antimicrobial resistance and mortality among adults and children with community-onset bacterial infections in India. The Journal of infectious diseases. 2017 Apr 15;215(8):1312-20.
15. Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Pérès A, Paris DH, Phetsouvanh R, Tangkhabuanbutra J, Douangdala P, Inthalath S, Souvannasing P, Slesak G. Causes of non-malarial fever in Laos: a prospective study. The Lancet Global Health. 2013 Jul 1;1(1):e46-54.
16. Mejia N, Pallas SW, Saha S, Udin J, Sayeed KI, Garrett DO, Date K, Abimbola T. Typhoid and paratyphoid cost of illness in Bangladesh: patient and health facility costs from the Surveillance for Enteric Fever in Asia Project II. Clinical Infectious Diseases. 2020 Nov 1;71(Supplement_3):S293-305.
17. Miah MT, Rahman S, Sarker CN, Khan GK, Barman TK. Study on 40 cases of rickettsia. Mymensingh medical journal: MMJ. 2007 Jan 1;16(1):85-8.
18. Moreira J, Bressan CS, Brasil P, Siqueira AM. Epidemiology of acute febrile illness in Latin America. Clinical Microbiology and Infection. 2018 Aug 1;24(8):827-35.

19. Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of severe febrile illness in low- and middle-income countries: a systematic review. PloS one. 2015 Jun 30;10(6):e0127962.
20. Rajsekhar P, Sudheendra K. Evaluation of Acute Febrile Illness in Patients Presenting to a Tertiary Care Hospital. Journal of Evolution of Medical and Dental Sciences. 2019;8(50):3801-4.
21. Ratsimbasoa A, Fanazava L, Radrianjafy R, Ramilijaona J, Rafanomezantsoa H, Ménard D. Evaluation of two new immunochromatographic assays for diagnosis of malaria. American Journal of Tropical Medicine and Hygiene. 2008 Nov 1;79(5):670.
22. Rhee C, Kharod GA, Schaad N, Furukawa NW, Vora NM, Blaney DD, Crump JA, Clarke KR. Global knowledge gaps in acute febrile illness etiologic investigations: A scoping review. PLoS neglected tropical diseases. 2019 Nov 15;13(11):e0007792.
23. Robinson ML, Kadam D, Khadse S, Balasubramanian U, Raichur P, Valvi C, Marbaniang I, Kanade S, Sachs J, Basavaraj A, Bharadwaj R. Vector-borne disease is a common cause of hospitalized febrile illness in India. The American journal of tropical medicine and hygiene. 2018 May;98(5):1526.
24. Saha S, Sayeed KI, Saha S, Islam MS, Rahaman A, Islam M, Rahman H, Das R, Hasan MM, Uddin MJ, Tanmoy AM. Hospitalization of pediatric enteric fever cases, Dhaka, Bangladesh, 2017–2019: incidence and risk factors. Clinical Infectious Diseases. 2020 Nov 1;71(Supplement_3):S196-204.
25. Sajib MS, Tanmoy AM, Hooda Y, Rahman H, Andrews JR, Garrett DO, Endtz HP, Saha SK, Saha S. Tracking the emergence of azithromycin resistance in multiple genotypes of typhoidal salmonella. MBio. 2021 Feb 23;12(1):10-128.
26. Sánchez-González L, Quandelacy TM, Johansson M, Torres-Velásquez B, Lorenzi O, Tavarez M, Torres S, Alvarado LI, Paz-Bailey G. Viral etiology and seasonal trends of pediatric acute febrile illness in southern Puerto Rico; a seven-year review. Plos one. 2021 Feb 19;16(2):e0247481.
27. Shrestha P, Dahal P, Ogbonnaa-Njoku C, Das D, Stepniewska K, Thomas NV, Hopkins H, Crump JA, Bell D, Newton PN, Ashley EA. Non-malarial febrile illness: a systematic review of published aetiological studies and case reports from Southern Asia and South-eastern Asia, 1980–2015. BMC medicine. 2020 Dec;18(1):1-4.
28. Tomashek KM, Lorenzi OD, Andújar-Pérez DA, Torres-Velasquez BC, Hunsperger EA, Munoz-Jordan JL, Perez-Padilla J, Rivera A, Gonzalez-Zeno GE, Sharp TM, Galloway RL. Clinical and epidemiologic characteristics of dengue and other etiologic agents among patients with acute febrile illness, Puerto Rico, 2012–2015. PLoS neglected tropical diseases. 2017 Sep 13;11(9):e0005859.
29. World Health Organization, Special Programme for Research, Training in Tropical Diseases, World Health Organization. Department of Control of Neglected Tropical Diseases, World Health Organization. Epidemic, Pandemic Alert. Dengue: guidelines for diagnosis, treatment, prevention and control. World Health Organization; 2009.