Introduction

In tropical countries such as India, the months of July–October see a huge upsurge in the number of patient admissions due to acute febrile illnesses (AFIs). These diseases have varied clinical courses ranging from spontaneous recovery to acute fatality. In a developing country like India, this results in a huge burden on all levels of healthcare. The triage of these patients has always been a challenging task, as there are very few studies on predictors of severe disease in patients with AFI without any specific diagnosis. Consequently, not all patients admitted in the lower levels of healthcare get timely referral. Even though individual predictors of severity for certain tropical fevers such as dengue and malaria have been proposed, it requires categorization of patients with AFI into individual diseases. The lack of properly functioning round the clock laboratory services further delays the diagnosis in such cases. The objective of this study was to identify the clinical and laboratory parameters, which are significantly associated with higher levels of care, while presence of arthralgia, serositis, and leucopenia indicated a higher likelihood of recovery with minimal support.

Materials and Methods

This was a retrospective review of records, whereby clinical and laboratory parameters of patients with AFI admitted in our tertiary care center between July 2016 and October 2016 were reviewed. Appropriate tests of significance were applied using SPSS 21 (Chicago, IL, USA) to find statistically significant differences between those who required mechanical ventilation, intensive care, inotropes, or higher intravenous antibiotics and those who recovered with minimal supportive care. Results: Presence of comorbidities, dyspnea, altered sensorium, features of myocarditis, hypotension, leukocytosis (>11,000/µL), and acute kidney injury were significantly associated with requirement of higher levels of care, while presence of arthralgia, serositis, and leucopenia indicated a higher likelihood of recovery with minimal support. Conclusion: This article highlights the possibility of identification of simple alarm signs in patients with AFI which would indicate the need for higher levels of care.
outcomes were recorded using a detailed proforma. Data were then entered into an Excel sheet. The patients were then divided into two groups. Group 1 consisted of those people who required mechanical ventilation, intensive care, ionotropic support, or higher intravenous antibiotics (betalactam/betalactamase inhibitor combination or carbapenems for more than 10 days). All others were grouped under group 2. Appropriate tests of significance were applied using SPSS 21(Chicago, IL, USA) to find statistically significant differences between the two groups.

Results

A total of 53 patients between the age range of 14 and 77 years with AFI (<15 days of fever) were admitted in our unit between July and October, 2016 (July 5, August 16, September 19, October 13). The patients were referred from various parts of North India (Delhi 37, Bihar 4, Haryana 6, Madhya Pradesh 1, Uttar Pradesh 3, West Bengal 2). Seven patients required care in the intensive care unit (ICU). The stay in ICU ranged between 2 and 23 days with a mean of 6 days. A total of 11 patients required mechanical ventilation.

Four of these patients developed ventilator-associated pneumonia. A total of 24 patients needed antibiotics during admissions. Among those who received antibiotics, the average duration of antibiotic administration was 7 ± 6 days. The following antibiotics were used for varying durations: ceftriaxone (n = 24), doxycycline (n = 13), levofloxacin (n = 13), ceftoperazone–sulbactam (n = 10), piperacillin–tazobactam (n = 9), clindamycin (n = 9), azithromycin (n = 9), vancomycin (n = 7), linezolid (n = 3), ticoplanin (n = 4), metronidazole (n = 3), amoxicillin–clavulanate (n = 3), amikacin (n = 2), and meropenem (n = 1). A total of 16 patients developed hypotension and 12 required ionotropic support. A total of 10 patients were either in sepsis at the time of admission or developed sepsis during the course of hospital stay. A total of eight patients died during the hospital stay. Platelet transfusion was required in 20 patients. The use of steroids was required in eight patients. Hematological and biochemical parameters of the patients are summarized in Table 1. The following diagnostic outcomes were observed on the basis of clinical features, microbiological investigations, and response to treatment: dengue (n = 17), chikungunya (n = 13), malaria (n = 6), community-acquired pneumonia (n = 5), scrub typhus (n = 3), malaria–dengue coinfection (n = 1), tubercular meningitis (n = 1), urinary tract infection (n = 3), dengue–chikungunya coinfection (n = 1), chicken pox (n = 1), and acute undifferentiated febrile illness (n=2).

The patients were divided into two groups; group 1 had 17 patients, while group 2 had 36 patients. The following parameters were more commonly seen in group 1 than in group 2: presence of comorbidities, dyspnea, altered sensorium, features of myocarditis, bleeding manifestations, hypotension, leukocytosis (>11,000/µL), and thrombocytopenia.

Table 1: Clinical and laboratory parameters of patients with acute febrile illness categorized into group 1 and group 2

| Parameters                     | Group 1 | Group 2 | P   |
|-------------------------------|---------|---------|-----|
| Age, years (mean)             | 44±19   | 31±14   | 0.023 |
| Sex                           | Male 11 (64%), female 6 (36%) | Male 25 (70%), female 11 (30%) | 0.730 |
| Comorbidities                 | 9 (53%) | 6 (44%) | 0.006 |
| Total duration of fever before admission (mean) | 6.24±3 | 6.17±3 | 0.590 |
| Myalgia                       | 7 (41%) | 22 (61%) | 0.174 |
| Headache                      | 5 (30%) | 16 (44%) | 0.296 |
| Arthralgia                    | 1 (6%)  | 19 (53%) | 0.001 |
| Rash                          | 2 (12%) | 5 (14%) | 0.831 |
| Dyspnea                       | 12 (71%) | 8 (22%) | 0.001 |
| Altered sensorium             | 6 (36%) | 1 (3%) | 0.001 |
| Abdominal pain                | 4 (24%) | 13 (36%) | 0.430 |
| Vomiting                      | 5 (30%) | 13 (36%) | 0.151 |
| Diarrhea                      | 2 (12%) | 3 (8%) | 0.638 |
| Myocarditis                   | 5 (30%) | 1 (3%) | 0.004 |
| Bleeding manifestations       | 2 (12%) | 9 (25%) | 0.267 |
| Hypotension                   | 12 (71%) | 4 (11%) | 0.000 |
| Rash                          | 2 (12%) | 5 (14%) | 0.831 |
| Icterus                       | 4 (24%) | 4 (11%) | 0.238 |
| Serositis                     | 2 (12%) | 16 (44%) | 0.019 |
| Hepatomegaly                  | 2 (12%) | 6 (17%) | 0.642 |
| Splenomegaly                  | 2 (12%) | 5 (14%) | 0.831 |
| Anemia                        | 11 (65%) | 13 (36%) | 0.051 |
| Leucopenia                    | 1 (6%)  | 14 (39%) | 0.013 |
| Leukocytosis                  | 15 (88%) | 8 (22%) | 0.000 |
| Thrombocytopenia              | 12 (71%) | 31 (86%) | 0.051 |
| Transaminitis                 | 14 (82%) | 28 (78%) | 0.701 |
| Requiring platelet transfusion| 3 (18%) | 17 (47%) | 0.038 |
| Acute kidney injury           | 13 (76%) | 3 (8%) | 0.00 |
acute kidney injury (AKI). The following parameters were more commonly seen in group 2: presence of arthralgia (large and small joint), serositis (pleural effusion or ascites or gall bladder edema) and leucopenia (<4000/µL). The mean age was significantly higher in group 1 than in group 2.

Discussion

Patients with AFIIs are more likely to encounter primary care physicians at the onset of their illness. Although most of these AFIIs are self-limiting, it is important for the primary care physicians to identify the ones that may require higher levels of care. Distinguishing low-risk from high-risk patients can be challenging. However, certain clinical features may point toward disease severity and help the physician promptly refer the patient to a higher center. Although there are studies predicting severity in individual diseases, there are no such studies on alarm signs for referral in adult patients presenting with fever. These alarm features could be useful especially in the months of monsoon in India when there is an outbreak of vector borne diseases (dengue, malaria, chikungunya) every year. Some of the patients at low risk end up being referred to a higher center, whereas some who actually require referral might be missed. In developing settings, the option of triage without the compulsion of diagnosis may avoid overwhelming the health system and help us in rationing the limited resources. The economic burden of dengue itself is huge in most parts of India. In an estimate, the average medical cost of a dengue case in 2012 was $235.20, if hospitalized.[8]

Higher age and presence of comorbidities were found to be significant factors indicating a requirement of higher levels of care. In a study from Kerala, age >40 years and presence of comorbidities were associated with higher mortality in dengue patients.[9] Similarly, in a study from Pakistan, increasing age in dengue was found to be a significant factor associated with prolonged stay.[10] Clinical features such as dyspnea, altered sensorium, features of myocarditis, and hypotension were indicative of the fact that the patient needed earlier referral. In a study from Taiwan, a lower Glasgow coma score was associated with higher mortality.[10] In a systematic review and meta-analysis, coma score, hypoglycemia, and shock were significant predictors of mortality.[9] In a study on adult patients with malaria from India, longer duration of fever, decreased urine output, jaundice, and altered sensorium were predictors of severe malaria.[10] In a study from Sierra Leone, hypotension was a significant predictor of mortality in all febrile patients.[11] Leukocytosis (>11,000/µL) and AKI were laboratory features that predicted the need for referral. AKI has been shown to be a predictor of mortality in dengue patients in other studies as well.[10] Acute respiratory distress syndrome and AKI were significant predictors of mortality in patients with scrub typhus in an Indian study.[12] In a study from Delhi, higher age, dyspnea, altered sensorium, and leukocytosis were significantly associated with severe disease/mortality. Presence of arthralgia and leucopenia was associated with milder variants of disease, probably because these features are more commonly associated with chikungunya (compared to dengue) which rarely has severe manifestations.[13]

Conclusion

This article highlights the possibility of identification of simple alarm signs in patients with AFI without a diagnosis. These alarm signs can be used by the primary care physicians to identify the need of higher levels of care in patients with AFIIs.

Limitations

This was a retrospective study with a very small sample size. There is a need for multicentric prospective studies with larger sample size study ranging over few seasons.

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Conflicts of interest

There are no conflicts of interest.

References

1. Singh R, Singh SP, Ahmad N. A study of etiological pattern in an epidemic of acute febrile illness during monsoon in a tertiary health care institute of Uttarakhand, India. J Clin Diagn Res 2014;8:MC01-3.
2. Tun ZM, Moorthy M, Linster M, Su YC, Coker RJ, Ooi EE, et al. Characteristics of acute febrile illness and determinants of illness recovery among adults presenting to Singapore primary care clinics. BMC Infect Dis 2016;16:612.
3. Md-Sani SS, Md-Noor J, Han WH, Gan SP, Rani NS, Tan HL, et al. Prediction of mortality in severe dengue cases. BMC Infect Dis 2018;18:232.
4. Kumar R, Saravu K. Severe vivax malaria: A prospective exploration at a tertiary healthcare centre in Southwestern India. Pathog Glob Health 2017;111:148-60.
5. Shepard DS, Halasa YA, Tyagi BK, Adhish SV, Nandan D, Karthiga KS, et al. Economic and disease burden of dengue illness in India. Am J Trop Med Hyg 2014;91:1235-42.
6. Karunakaran A, Ilyas WM, Sheen SF, Jose NK, Nujum ZT. Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India. J Infect Public Health 2014;7:114-20.
7. Khalil MA, Tan J, Khalil MAU, Awan S, Rangasami M. Predictors of hospital stay and mortality in dengue virus infection - Experience from Aga Khan University Hospital Pakistan. BMC Res Notes 2014;7:473.
8. Chen CM, Chen KS, Yu WL, Cheng KC, Chao HC, Yeh CY, et al. The outcomes of patients with severe dengue admitted to intensive care units. Medicine (Baltimore) 2016;95:e4376.
9. Sypniewska P, Duda JF, Locatelli I, Althaus CR, Althaus F, Genton B. Clinical and laboratory predictors of death in African children with features of severe malaria: A systematic review and meta-analysis. BMC Med 2017;15:147.
10. Gupta BK, Gupta A, Nehra HR, Balotia HR, Meena SL, Kumar S. Clinical profile and prognostic indicators in...
adults hospitalized with severe malaria caused by different plasmodium species. Infect Dis (Auckl) 2015;8:45-50.

11. Roth PJ, Grant DS, Ngegbai AS, Schieffelin J, McClelland RS, Jarrett OD. Factors associated with mortality in febrile patients in a government referral hospital in the Kenema district of Sierra Leone. Am J Trop Med Hyg 2015;92:172-7.

12. Bhargava A, Kaushik R, Kaushik RM, Sharma A, Ahmad S, Dhar M, et al. Scrub typhus in Uttarakhand & adjoining Uttar Pradesh: Seasonality, clinical presentations & predictors of mortality. Indian J Med Res 2016;144:901-9.

13. Paternina-Caicedo A, De la Hoz-Restrepo F, Díaz-Quijano F, Caicedo-Torres W, Auxiliadora Badillo-Viloria M, Bula-Anichiarico D, et al. Features of dengue and chikungunya infections of Colombian children under 24 months of age admitted to the emergency department. J Trop Pediatr 2018;64:31-7.