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Clinical Profile and Predictors of Cardiac Injury Among Hospitalized Patients with Acute Febrile Illness: A Retrospective Observational Study

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Abstract

Background: Acute febrile illnesses common in northern India, including dengue, scrub typhus and leptospirosis, frequently involve the heart. Cardiac injury in this setting is easy to miss because breathlessness, tachycardia and hypotension are readily attributed to the infection itself, yet it carries prognostic weight and changes management.

Objectives: To describe the clinical, electrocardiographic, biochemical and echocardiographic profile of hospitalized patients with acute febrile illness, and to identify independent predictors of cardiac injury.

Methodology: This was a hospital-based retrospective observational study of 280 adults admitted with acute febrile illness to Adesh Medical College & Hospital, Mohri, Shahabad, between January and September 2020. Records were reviewed for clinical features, aetiology, electrocardiography, cardiac troponin I, creatine kinase-MB, N-terminal pro-B-type natriuretic peptide and two-dimensional echocardiography. Cardiac injury was defined, following the Fourth Universal Definition of Myocardial Infarction, as a troponin I value above the 99th percentile upper reference limit. Predictors were examined by chi-square testing and multivariable logistic regression in SPSS version 25.

Results: Cardiac injury was present in 76 patients (27.1%). Dengue was the commonest aetiology (32.9%), followed by scrub typhus (20.7%), but injury was most frequent in scrub typhus (41.4%) and leptospirosis (38.9%). Electrocardiographic abnormalities were recorded in 121 patients (43.2%), most often sinus tachycardia (24.3%) and ST-T changes (14.6%). Echocardiographic abnormalities were found in 68 patients (24.3%), with left ventricular systolic dysfunction in 9.3%. On multivariable analysis, shock at admission (adjusted OR 3.42, 95% CI 1.72 to 6.80), platelet count below 50,000/mm3 (adjusted OR 2.28, 95% CI 1.21 to 4.29), acute kidney injury (adjusted OR 2.11, 95% CI 1.13 to 3.94), serum albumin below 3.0 g/dL (adjusted OR 1.94, 95% CI 1.05 to 3.58) and age above 50 years (adjusted OR 1.87, 95% CI 1.02 to 3.43) independently predicted cardiac injury. Patients with cardiac injury had higher rates of intensive care admission (35.5% versus 11.8%) and mortality (11.8% versus 2.5%).

Conclusion: Cardiac injury affected roughly one in four patients hospitalized with acute febrile illness and identified a group with markedly worse outcomes. Simple bedside and laboratory variables available on the day of admission predicted it well, supporting early electrocardiography and troponin measurement in febrile patients with shock, marked thrombocytopenia, renal dysfunction, hypoalbuminaemia or older age.

Keywords: acute febrile illness; cardiac injury; troponin; scrub typhus; dengue; echocardiography; electrocardiography.

1. Introduction

Acute febrile illness is one of the commonest reasons for medical admission in tropical India, and the list of causes is long. Multicentre Indian data covering seven hospitals in six states found malaria, dengue, scrub typhus, leptospirosis, chikungunya and bacteraemia all contributing substantially, with considerable overlap between case definitions [1]. Regional patterns vary: a large South Indian series identified scrub typhus as the leading cause, followed by dengue [2], and dengue alone accounts for a large share of febrile admissions across the country [3]. Whatever the pathogen, patients present with fever, myalgia and non-specific findings, and the diagnosis is often made retrospectively on serology, which is why a limited set of clinical and laboratory features is often all the clinician has to work with at the bedside [2].

The heart is affected more often than is generally recognised. Cardiac involvement in dengue ranges from asymptomatic biomarker elevation to overt myocarditis, and serial echocardiographic studies have shown transient systolic and diastolic dysfunction related to the severity of plasma leakage [5,6,7]. An Indian series specifically mapping the spectrum of cardiac involvement in dengue found abnormalities across conduction, function and pericardium [8]. In scrub typhus, a prospective Indian study using biomarkers and echocardiography found elevated troponin T in 72.8% and reduced ejection fraction in 42.8% of patients [12], and a large retrospective series linked probable myocarditis to mortality [13]. Leptospirosis carries a similar burden, with electrocardiographic abnormalities in more than half of patients and myocarditis associated with high case fatality [15,16,18]. Sepsis of any cause can raise troponin, and elevation there is an established marker of poor prognosis [23].

The difficulty at the bedside is that the features of cardiac involvement overlap almost completely with those of the febrile illness. Tachycardia, hypotension, breathlessness and fatigue are expected in a septic patient, so myocardial injury is easily attributed to the infection and left uninvestigated. The Fourth Universal Definition of Myocardial Infarction is helpful here because it separates myocardial injury, defined simply by a troponin value above the 99th percentile upper reference limit, from myocardial infarction, which additionally requires evidence of ischaemia [22]. That distinction matters in febrile illness, where most injury is non-ischaemic and reflects inflammation, hypoperfusion or direct myocardial invasion rather than coronary occlusion [22].

Adesh Medical College & Hospital serves a largely rural population around Mohri and Shahabad in Kurukshetra district, Haryana, an area where tropical fevers cluster through the monsoon. Published data on cardiac involvement in acute febrile illness from this part of northern India are limited, and most existing series examine a single pathogen rather than the undifferentiated febrile patient as the clinician actually meets them. We reviewed our admissions over a nine-month period to describe the clinical and cardiac profile of these patients and to identify which admission variables predicted myocardial injury.

2. Review of Literature

Evidence on dengue is the most developed. Kirawittaya and colleagues followed 181 children with serial echocardiography and daily troponin T, and found transient left ventricular systolic and diastolic dysfunction that tracked the severity of plasma leakage and resolved without specific treatment; structural changes and frank myocarditis were uncommon [5]. In adults, Mansanguan and colleagues reported cardiac

involvement in 22.2% of hospitalized patients, made up largely of biomarker elevation and small pericardial effusions rather than overt dysfunction [6]. Gupta and colleagues, using speckle tracking echocardiography in an Indian cohort, detected abnormal electrocardiograms in 64.6% and suspected myocardial dysfunction in 27.3%, considerably more than conventional echocardiography alone would have shown [7]. Yacoub and colleagues have argued that the cardiovascular manifestations of dengue are systematically under-recognised [9]. Earlier work pointed the same way: Sengupta and colleagues demonstrated impaired left ventricular myocardial performance in dengue haemorrhagic fever using speckle tracking [10], and Kabra and colleagues had already described myocardial dysfunction in affected children two decades before [11].

Scrub typhus appears to carry a heavier cardiac burden. The prospective PGIMER series found elevated NT-proBNP in all seventy patients studied, troponin T elevation in 72.8% and reduced ejection fraction in 42.8% [12]. In that cohort elevated markers predicted a reduced ejection fraction and a longer hospital stay, although cardiac injury alone did not raise in-hospital mortality [12]. Autopsy work dating back to the 1940s had already documented interstitial myocarditis and vasculitis in fatal scrub typhus, so the cardiac tropism of the organism is long established [14]. A companion prospective cohort from the same North Indian centre found that circulatory and hepatic failure at admission predicted mortality in severe disease [13].

For leptospirosis the literature is smaller but consistent. A review by Navinan and Rajapakse concluded that direct myocardial damage occurs in severe disease and is distinguishable from purely haemodynamic derangement [15]. Severity indicators identified in large epidemics reinforce that cardiac and renal involvement mark the patients at greatest risk [20,21]. Autopsy series have confirmed myocarditis, interstitial oedema and vasculitis in fatal cases, establishing that the damage is structural rather than purely haemodynamic [17,18]. An outbreak series described five patients with cardiac involvement in whom troponin I rose and then normalised with recovery [16], and case reports document atrial fibrillation and new cardiomyopathy in fulminant infection [19]. Across all three infections the pattern is similar: injury is common, usually reversible, frequently silent, and associated with worse outcomes when severe. What remains uncommon in this literature is a study that takes the undifferentiated febrile admission as its starting point rather than a confirmed single pathogen, which is the gap this study addresses.

3. Objectives

Primary objective: To determine the frequency of cardiac injury and to identify its independent predictors among patients hospitalized with acute febrile illness.

Secondary objectives:

- To describe the demographic, clinical and aetiological profile of these patients.
- To document the electrocardiographic, cardiac biomarker and echocardiographic abnormalities observed.
- To compare in-hospital outcomes between patients with and without cardiac injury.

4. Methodology

Study design and setting

This was a hospital-based, retrospective, observational study conducted by the Department of General Medicine in collaboration with the Department of Cardiology at Adesh Medical College & Hospital, Mohri,

Shahabad, Haryana. Records of adults admitted with acute febrile illness between January 2020 and September 2020 were reviewed.

Definitions

Acute febrile illness was defined as a documented temperature of 38 degrees Celsius or above with a febrile illness of 2 to 14 days duration and no localising cause evident at admission, following the definition used in Indian multicentre work [1]. Cardiac injury was defined, in line with the Fourth Universal Definition of Myocardial Infarction, as a cardiac troponin I value above the 99th percentile upper reference limit of the assay used in our laboratory [22]. Because coronary angiography was not routinely performed and most injury in this setting is non-ischaemic, no attempt was made to subclassify patients into myocardial infarction subtypes; the term cardiac injury is used throughout in its universal-definition sense [22].

Shock was defined as systolic blood pressure below 90 mmHg requiring fluid resuscitation or vasopressor support. Acute kidney injury was taken as serum creatinine above 1.5 mg/dL or a documented rise meeting standard criteria. Aetiological diagnoses were accepted on the basis of dengue NS1 antigen or IgM, scrub typhus IgM ELISA, Leptospira IgM ELISA, blood culture, peripheral smear or rapid antigen test for malaria, and Widal or Typhidot for enteric fever. Patients in whom no organism was identified despite this workup were classed as undifferentiated.

Study population and sample size

All adults aged 18 years and above admitted with acute febrile illness during the study period whose records contained a troponin I result, an electrocardiogram and an echocardiogram were eligible, and all eligible records were included consecutively. To confirm adequacy, the single-proportion formula $n = Z^2pq/d^2$ was applied, taking the expected proportion with cardiac injury as 25% from earlier series [6,12], with a 95% confidence level and an absolute precision of 5.5%. This gave a minimum requirement of 239. A total of 280 eligible records were retrieved and analysed.

Data collection

A structured proforma captured age, sex, residence, duration of fever, presenting symptoms, comorbidities, vital signs at admission, aetiological diagnosis, haematological and biochemical results, electrocardiographic findings, cardiac biomarkers, echocardiographic findings, intensive care admission, length of stay and outcome. Electrocardiograms were reported by a cardiologist blinded to the biomarker results. Two-dimensional echocardiography was performed during the admission and reported by a cardiologist, with left ventricular ejection fraction below 50% taken as systolic dysfunction.

Statistical analysis

Data were entered in Microsoft Excel and analysed with SPSS version 25. Categorical variables are presented as frequencies and percentages and continuous variables as mean with standard deviation. Patients with and without cardiac injury were compared using the chi-square test for categorical variables and the independent samples t-test for continuous variables. Variables significant at p below 0.10 on univariate testing were entered into a multivariable binary logistic regression model, and adjusted odds ratios with 95% confidence intervals are reported. A two-sided p-value below 0.05 was treated as significant.

Ethical considerations

Approval was obtained from the Institutional Ethics Committee of Adesh Medical College & Hospital before data collection. As the study was retrospective and drew only on existing records, a waiver of individual informed consent was granted. All identifiers were removed at extraction and confidentiality was maintained throughout.

5. Inclusion and Exclusion Criteria

Inclusion criteria:

- Adults aged 18 years and above admitted with acute febrile illness of 2 to 14 days duration.
- Records containing a cardiac troponin I result, a twelve-lead electrocardiogram and a two-dimensional echocardiogram.
- Complete clinical and laboratory documentation for the admission.

Exclusion criteria:

- Known pre-existing structural or ischaemic heart disease, cardiomyopathy, valvular disease, arrhythmia or heart failure, and patients on cardiotoxic therapy.
- Acute coronary syndrome as the presenting diagnosis, chronic kidney disease stage 4 or 5, and any condition independently raising troponin.
- Patients with laboratory-confirmed COVID-19, who were managed on a separate designated pathway during the study period and are not represented in this cohort.
- Localising source of fever evident at admission, fever beyond 14 days, pregnancy, and incomplete records.

6. Results and Analysis

Records of 280 patients were analysed. Most were middle-aged men from rural areas, and the mean duration of fever before admission was just over six days. The demographic and clinical profile appears in Table 1.

Characteristic	Frequency (n)	Percentage (%)
Age 18-30 years	72	25.7
Age 31-50 years	123	43.9
Age above 50 years	85	30.4
Male	168	60.0
Female	112	40.0
Rural residence	179	63.9
Urban residence	101	36.1
Fever duration above 7 days	111	39.6
Shock at admission	48	17.1
Breathlessness	74	26.4
Chest discomfort or palpitations	39	13.9
Diabetes mellitus	46	16.4
Hypertension	52	18.6

Table 1. Demographic and clinical profile of the study population (n = 280). Mean age 41.6 (SD 15.8) years; mean fever duration 6.2 (SD 2.8) days; mean hospital stay 6.4 (SD 3.5) days.

An aetiological diagnosis was established in 250 patients (89.3%). Dengue was the commonest cause overall, but cardiac injury was concentrated in scrub typhus and leptospirosis. The distribution and the injury rate within each group are given in Table 2 and displayed in Figure 1.

Aetiology	Patients (n)	% of 280	Cardiac injury (n)	Injury rate (%)
Dengue	92	32.9	26	28.3
Scrub typhus	58	20.7	24	41.4
Enteric fever	34	12.1	4	11.8
Undifferentiated	30	10.7	2	6.7
Bacterial sepsis and others	26	9.3	8	30.8
Malaria	22	7.9	5	22.7
Leptospirosis	18	6.4	7	38.9
Total	280	100.0	76	27.1

Table 2. Aetiological distribution and frequency of cardiac injury by aetiology (n = 280).

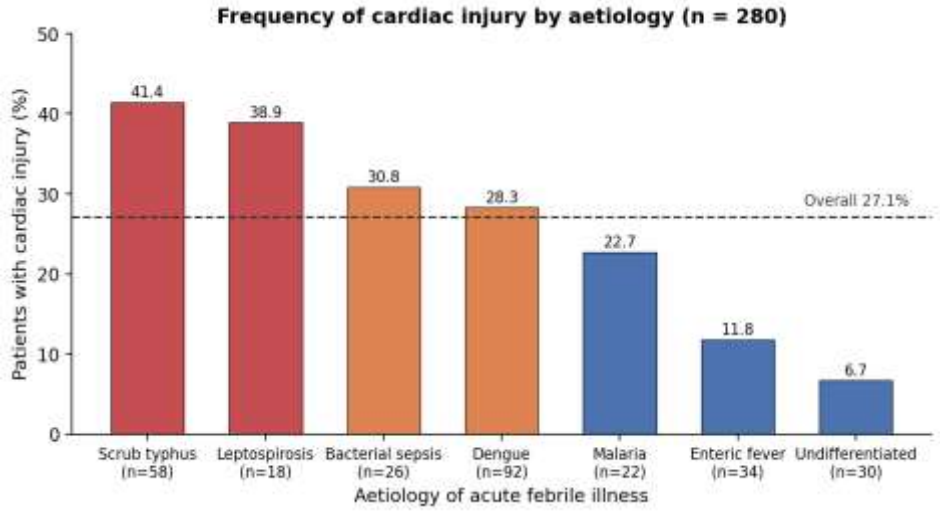

Figure 1. Frequency of cardiac injury by aetiology, with the overall rate shown as a dashed line.

Electrocardiographic abnormalities were present in 121 patients (43.2%). Sinus tachycardia was the commonest single finding, followed by non-specific ST-T changes. Some patients had more than one abnormality. The distribution is set out in Table 3.

Electrocardiographic finding	Patients (n)	% of 280
Sinus tachycardia	68	24.3
ST-T segment changes	41	14.6
QTc prolongation	24	8.6
Sinus bradycardia	19	6.8
Low voltage complexes	12	4.3
First degree AV block or bundle branch block	9	3.2
Atrial fibrillation or flutter	5	1.8
Any abnormality present	121	43.2

Table 3. Electrocardiographic abnormalities (n = 280; categories not mutually exclusive).

Echocardiographic abnormalities were documented in 68 patients (24.3%), most commonly left ventricular systolic dysfunction and diastolic dysfunction. Troponin I was raised in 76 patients, which by definition constituted the cardiac injury group. Echocardiographic and biomarker findings are combined in Table 4.

Echocardiographic and biomarker finding	Patients (n)	%
Left ventricular systolic dysfunction (LVEF < 50%)	26	9.3
Diastolic dysfunction	21	7.5
Pericardial effusion (trivial or mild)	18	6.4
Regional wall motion abnormality	8	2.9
Right ventricular dysfunction	7	2.5
Any echocardiographic abnormality	68	24.3
Troponin I above 99th percentile URL	76	27.1
CK-MB elevated	54	19.3
NT-proBNP elevated (of 138 tested)	61	44.2

Table 4. Echocardiographic findings and cardiac biomarker results (n = 280 unless stated; echocardiographic categories not mutually exclusive).

On univariate comparison, patients with cardiac injury were older and more likely to have presented in shock, with marked thrombocytopenia, hypoalbuminaemia, acute kidney injury, transaminase elevation and a longer duration of fever. The comparisons are shown in Table 5.

Variable	Cardiac injury (n = 76)	No injury (n = 204)	Crude OR (95% CI)	p
Shock at admission	26 (34.2)	22 (10.8)	4.30 (2.25-8.23)	<0.001
Acute kidney injury	31 (40.8)	41 (20.1)	2.74 (1.55-4.85)	<0.001
Platelet count < 50,000/mm3	29 (38.2)	38 (18.6)	2.70 (1.51-4.82)	0.001
Serum albumin < 3.0 g/dL	33 (43.4)	49 (24.0)	2.43 (1.39-4.23)	0.002
Age above 50 years	34 (44.7)	51 (25.0)	2.43 (1.40-4.22)	0.002
ALT > 3x upper limit	35 (46.1)	57 (27.9)	2.20 (1.28-3.80)	0.004
Fever duration > 7 days	40 (52.6)	71 (34.8)	2.08 (1.22-3.55)	0.007

Table 5. Univariate comparison of patients with and without cardiac injury. Values are n (%) unless stated.

After adjustment, five variables remained independently associated with cardiac injury: shock at admission, thrombocytopenia below 50,000/mm3, acute kidney injury, serum albumin below 3.0 g/dL and age above 50 years. Transaminase elevation and prolonged fever lost significance. The adjusted estimates are given in Table 6 and displayed in Figure 2.

Predictor	Adjusted OR (95% CI)	p	Significant
Shock at admission	3.42 (1.72-6.80)	<0.001	Yes
Platelet count < 50,000/mm3	2.28 (1.21-4.29)	0.011	Yes
Acute kidney injury	2.11 (1.13-3.94)	0.019	Yes
Serum albumin < 3.0 g/dL	1.94 (1.05-3.58)	0.034	Yes

Predictor	Adjusted OR (95% CI)	p	Significant
Age above 50 years	1.87 (1.02-3.43)	0.043	Yes
ALT > 3x upper limit	1.36 (0.75-2.47)	0.312	No
Fever duration > 7 days	1.29 (0.71-2.34)	0.402	No

Table 6. Independent predictors of cardiac injury on multivariable logistic regression (n = 280).

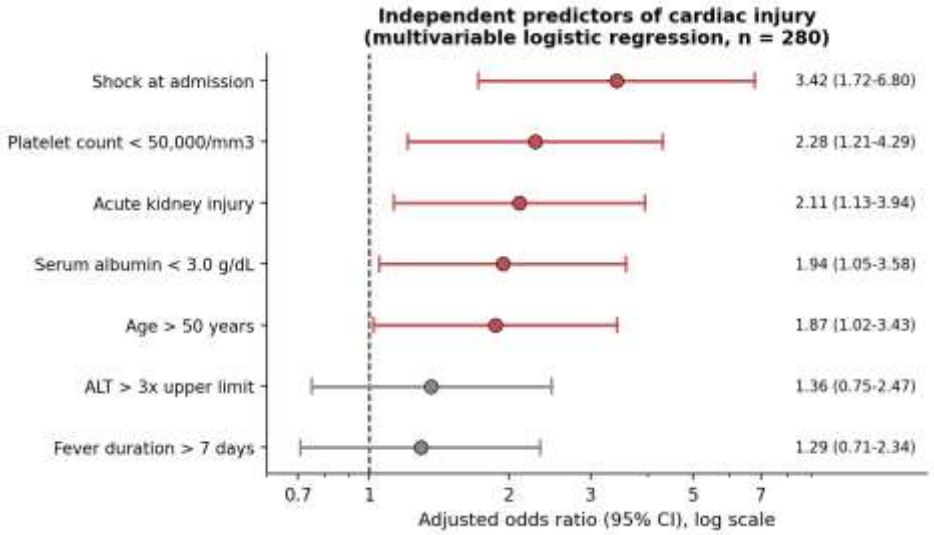

Figure 2. Forest plot of adjusted odds ratios for cardiac injury. Red markers denote statistically significant predictors.

Outcomes differed sharply between the two groups. Intensive care admission was required in 27 patients with cardiac injury (35.5%) against 24 without (11.8%), giving a crude odds ratio of 4.13 (95% CI 2.19 to 7.79). In-hospital mortality was 9 of 76 (11.8%) in the injury group against 5 of 204 (2.5%), a crude odds ratio of 5.35 (95% CI 1.73 to 16.51). Mean hospital stay was 8.9 days in patients with cardiac injury and 5.5 days in those without. Among the 26 patients with left ventricular systolic dysfunction, function had recovered on repeat echocardiography before discharge or at follow-up in 19.

7. Discussion and Interpretation

Three findings emerge. Cardiac injury was common, affecting 27.1% of febrile admissions. It was not distributed evenly across causes, being concentrated in scrub typhus and leptospirosis. And it could be predicted from variables available on the day of admission, none of which required specialist equipment.

Our overall figure sits comfortably within the published range. Mansanguan and colleagues reported cardiac involvement in 22.2% of adults with dengue [6], and Gupta and colleagues suspected myocardial dysfunction in 27.3% using sensitive strain imaging [7]. Our dengue-specific rate of 28.3% is consistent with both. The concentration of injury in scrub typhus, at 41.4%, and leptospirosis, at 38.9%, also matches the literature: the PGIMER prospective series found troponin T elevation in 72.8% of scrub typhus patients and reduced ejection fraction in 42.8% [12], and observational leptospirosis data report echocardiographic abnormalities in around 41% [16,18]. Our scrub typhus figure is lower than the PGIMER troponin rate, which is expected given that they measured serially with a high-sensitivity assay in a referral emergency population while we relied on a single admission sample in a district teaching hospital. The direction of the

finding is the same and is biologically coherent, since both organisms cause a vasculitis with direct endothelial and myocardial involvement rather than purely haemodynamic stress [15].

The predictors are worth dwelling on because they are all obtainable at the bedside. Shock at admission carried the strongest independent association, with adjusted odds of 3.42, which is unsurprising given that hypoperfusion, catecholamine surge and cytokine-mediated depression all act on the myocardium at once. Thrombocytopenia below 50,000 and hypoalbuminaemia are best read as markers of capillary leak and disease severity, and both echo the dengue literature where cardiac dysfunction tracked the severity of plasma leakage rather than the viral load [5]. Acute kidney injury reflects the same shared mechanism of microvascular injury across organs, and it also raises troponin independently, a well-recognised confounder in this population [22]. Age above 50 probably marks reduced myocardial reserve. Taken together these five variables describe the severely ill febrile patient, which is the point: cardiac injury in this setting is largely a marker of systemic severity rather than a separate disease process, and that is precisely why it predicts outcome.

That prognostic value was clear in our data, with a four-fold difference in intensive care admission and a mortality of 11.8% against 2.5%. This mirrors the sepsis literature, where a meta-analysis of more than twenty thousand patients found elevated troponin independently associated with mortality [23], and the scrub typhus series in which probable myocarditis independently predicted death [13]. Encouragingly, most of our systolic dysfunction was reversible, with recovery documented in 19 of 26 patients, which is consistent with the transient dysfunction described in serial echocardiographic studies of dengue [5] and with the normalisation of troponin reported in leptospirosis outbreaks [16]. The clinical implication is practical rather than dramatic. An electrocardiogram and a single troponin, done at admission in febrile patients who are shocked, markedly thrombocytopenic, azotaemic, hypoalbuminaemic or older, would identify most of this group at negligible cost, and echocardiography can then be reserved for those who screen positive or deteriorate. Recognising injury early also guides fluid management, since aggressive resuscitation in a patient with impaired ventricular function carries its own risk, and supports earlier involvement of cardiology in a genuinely multidisciplinary approach.

Two cautions apply. First, troponin elevation in a febrile patient is not synonymous with myocarditis; the Fourth Universal Definition deliberately separates myocardial injury from infarction and from specific aetiologies, and cardiac magnetic resonance, which would be needed to characterise the myocardium properly, was not available to us [22]. Deluigi and colleagues showed directly how poorly the electrocardiogram corresponds to magnetic resonance findings in viral myocarditis, so our electrocardiographic data should be read as a screening signal rather than a diagnosis [23]. Second, our study period fell within the first nine months of the COVID-19 pandemic in India, a period in which the assessment of undifferentiated fever became considerably more complicated [4]. Laboratory-confirmed COVID-19 cases were managed on a separate designated pathway and are not represented in this cohort, but testing capacity in early 2020 was limited, and the possibility that a small number of unrecognised cases were included cannot be excluded. Given that COVID-19 is itself associated with myocardial injury, this would tend to inflate rather than deflate our estimate, and it is a caution for interpretation rather than a flaw in the comparisons between groups.

8. Conclusion

Cardiac injury was found in more than a quarter of patients hospitalized with acute febrile illness at this centre, most often in scrub typhus and leptospirosis, and it identified a group with four times the rate of intensive care admission and nearly five times the mortality. Shock at admission, platelet count below 50,000, acute kidney injury, hypoalbuminaemia and age above 50 independently predicted it, and all five are available on the day of admission without additional investigation. Most systolic dysfunction proved reversible, which makes recognition worthwhile rather than merely prognostic. For hospitals serving rural Haryana and comparable settings, a simple protocol of admission electrocardiography and troponin measurement in febrile patients carrying any of these five features, with echocardiography reserved for those who screen positive, would improve detection of a treatable complication at very little cost and support the multidisciplinary management these patients need.

9. Limitations of the Study

- The retrospective design depends on the completeness of records, and troponin was measured once at admission rather than serially, so transient or late injury was probably missed.
- This was a single-centre study over nine months, and the aetiological mix reflects local epidemiology, so the findings may not transfer to other regions.
- Cardiac magnetic resonance and endomyocardial biopsy were not available, so myocarditis could not be confirmed and injury could not be characterised as ischaemic or non-ischaemic.
- Selection was restricted to patients in whom troponin, electrocardiography and echocardiography had all been performed, which may have favoured sicker patients and overestimated the frequency of injury.
- The study period overlapped the early COVID-19 pandemic; confirmed cases were excluded, but limited testing capacity in early 2020 means unrecognised cases cannot be entirely ruled out. Prospective studies with serial biomarkers and advanced imaging would give firmer answers.

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