

**ANTI NUCLEAR ANTIBODY EXPRESSION AND ITS RELATIONSHIP TO  
SEVERITY OF ILLNESS, ORGAN DYSFUNCTION AND OUTCOMES IN  
SCRUB TYPHUS**

---

**A dissertation submitted in partial fulfilment of the MD Branch- I (General Medicine) Examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai, to be held in April, 2015.**

## **CERTIFICATE**

This is to certify that the dissertation titled “ Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus” is the bonafide original work of Dr.Maria Koshy K, submitted in partial fulfilment of the M.D. Branch- I (General Medicine) Degree Examination to be conducted by the Tamil Nadu Dr.M.G.R Medical University, Chennai, Tamil Nadu in April, 2015.

Signature:

Guide:

Dr.Reginald Alex,

Professor,

Department of Medicine,

Christian Medical College, Vellore- 632004

## **CERTIFICATE**

This is to certify that the dissertation titled “ Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus” is the bonafide original work of Dr.Maria Koshy K, submitted in partial fulfilment of the M.D. Branch- I (General Medicine) Degree Examination to be conducted by the Tamil Nadu Dr.M.G.R Medical University, Chennai, Tamil Nadu in April, 2015.

Signature:

Dr.Anand Zachariah,  
Professor and Head,  
Department of Medicine,  
Christian Medical College, Vellore- 632004

## **CERTIFICATE**

This is to certify that the dissertation titled “ Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus” is the bonafide original work of Dr.Maria Koshy K, submitted in partial fulfilment of the M.D. Branch- I (General Medicine) Degree Examination to be conducted by the Tamil Nadu Dr.M.G.R Medical University, Chennai, Tamil Nadu in April, 2015.

Signature:

Dr.Alfred Job Daniel

Principal,

Christian Medical College, Vellore- 632004

## **ACKNOWLEDGEMENTS**

It gives me pleasure to express my gratitude to my respected teacher and guide, Professor Reginald Alex for his valuable suggestions, support and encouragement in carrying out this study.

I am also very grateful to Dr. J.V. Peter for his guidance, support and ideas for the study.

I would like to thank Dr. John Antony Jude, Department of Microbiology and Dr. John Mathew, Department of Rheumatology for their valuable suggestions and guidance.

I am grateful to Mrs. Visali, Department of Biostatistics, who helped me with data analysis.

I am thankful to all my patients for their kind co-operation.



**INSTITUTIONAL REVIEW BOARD (IRB)**  
**CHRISTIAN MEDICAL COLLEGE**  
VELLORE 632 002, INDIA

**Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)**  
Director, Christian Counselling Centre  
Chairperson, Ethics Committee

**Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho**  
Chairperson, Research Committee & Principal

**Dr. Nihal Thomas**  
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)  
Secretary, Ethics Committee, IRB  
Additional Vice Principal (Research)

March 18, 2013

Dr. Maria Koshy  
PG Senior Registrar  
Department of General Medicine  
Christian Medical College  
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**  
Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in scrub typhus.  
Dr. Maria Koshy, General Medicine, Dr. Reginald Alex, Dr. JV Peter,  
General Medicine, Dr. John Mathew, Clinical Immunology and Rheumatology,  
Dr. John Jude, Microbiology.

Ref: IRB Min. No. 8158 dated 09.01.2013

Dear Dr. Maria Koshy,

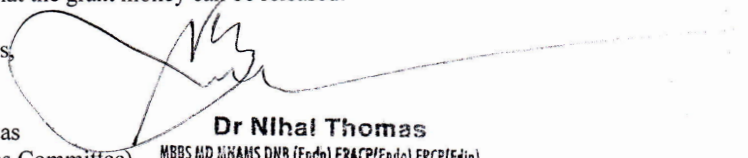
I enclose the following documents:-

1. Institutional Review Board approval
2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas  
Secretary (Ethics Committee)  
Institutional Review Board

  
**Dr Nihal Thomas**  
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)  
Secretary (Ethics Committee)  
Institutional Review Board

CC: Dr. Reginald Alex, Department of General Medicine, CMC



**INSTITUTIONAL REVIEW BOARD (IRB)**  
**CHRISTIAN MEDICAL COLLEGE**  
VELLORE 632 002, INDIA

**Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)**  
Director, Christian Counselling Centre  
Chairperson, Ethics Committee

**Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho**  
Chairperson, Research Committee & Principal

**Dr. Nihal Thomas**  
MD,MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)  
Secretary, Ethics Committee, IRB  
Additional Vice Principal (Research)

March 18, 2013

Dr. Maria Koshy  
PG Senior Registrar  
Department of General Medicine  
Christian Medical College  
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**  
Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in scrub typhus.  
Dr. Maria Koshy, General Medicine, Dr. Reginald Alex, Dr. JV Peter, General Medicine, Dr. John Mathew, Clinical Immunology and Rheumatology, Dr. John Jude, Microbiology.

Ref: IRB Min. No. 8158 dated 09.01.2013

Dear Dr. Maria Koshy,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in scrub typhus." on January 09, 2013.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Questionnaire
3. Information Sheet and Consent Form (English, Tamil, Telegu and Hindi)
4. Cvs of Drs. Maria Koshy, John Mathew, Reginald George Alex Tharmaraj, John Antony Jude Prakash, Peter John Victor.
5. A CD containing documents 1 – 4



**INSTITUTIONAL REVIEW BOARD (IRB)**  
**CHRISTIAN MEDICAL COLLEGE**  
VELLORE 632 002, INDIA

**Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)**  
Director, Christian Counselling Centre  
Chairperson, Ethics Committee

**Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho**  
Chairperson, Research Committee & Principal

**Dr. Nihal Thomas**  
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)  
Secretary, Ethics Committee, IRB  
Additional Vice Principal (Research)

The following Institutional Review Board (Research & Ethics Committee) members were present at the meeting held on January 9, 2013 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
Dr. Susanne Abraham	MBBS, MD	Professor, Dermatology, Venerology & Leprosy, CMC.	Internal, Clinician
Dr. Benjamin Perakath	MBBS, MS, FRCS	Professor, Surgery (Colorectal), CMC.	Internal, Clinician
Dr. Ranjith K Moorthy	MBBS MCh	Professor, Neurological Sciences, CMC	Internal, Clinician
Dr. P. Prasanna Samuel	B.Sc, M.Sc, PhD	Professor Dept. of Biostatistics, CMC	Internal, Statistician
Dr. Balamugesh	MBBS, MD(Int Med), DM, FCCP (USA)	Professor, Dept. of Pulmonary Medicine, CMC.	Internal, Clinician
Dr. Simon Rajaratnam	MBBS, MD, DNB (Endo), MNAMS (Endo), PhD (Endo), FRACP	Professor, Endocrinology, CMC	Internal, Clinician
Dr. AnupRamachandran	PhD	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
Dr. Chandrasingh	MS, MCH, DMB	Urology, CMC	Internal, Clinician
Dr. Paul Ravindran	PhD, Dip RP, FCCPM	Professor, Radiotherapy, CMC	Internal





**INSTITUTIONAL REVIEW BOARD (IRB)**  
**CHRISTIAN MEDICAL COLLEGE**  
VELLORE 632 002, INDIA

**Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)**  
Director, Christian Counselling Centre  
Chairperson, Ethics Committee

**Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho**  
Chairperson, Research Committee & Principal

**Dr. Nihal Thomas**  
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)  
Secretary, Ethics Committee, IRB  
Additional Vice Principal (Research)

Dr. Anand Zachariah	MBBS, MD, DNB	Professor, Dept. of Medicine, CMC	Internal, Clinician
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay Person
Mr. Sampath	BSc, BL	Advocate	External, Legal Expert
Mr. Harikrishnan	BL	Lawyer, Vellore	External, Legal Expert
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL	Legal Advisor, CMC.	Internal, Legal Expert
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	Internal, Social Scientist
<b>Dr. B. J. Prashantham (Chairperson), IRB Blue Internal</b>	<b>MA (Counseling), MA (Theology), Dr Min(Clinical)</b>	<b>Chairperson(IRB)&amp; Director, Christian Counselling Centre</b>	<b>External, Scientist</b>
Dr. JayaprakashMulyil	BSC, MBBS, MD, MPH, DrPH(Epid), DMHC	Retired Professor, Vellore	External, Scientist
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	Internal, Clinician

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent. And on completion of the study you are expected to submit a copy of the final report.



**INSTITUTIONAL REVIEW BOARD (IRB)**  
**CHRISTIAN MEDICAL COLLEGE**  
VELLORE 632 002, INDIA

**Dr. B J Prashantham, M.A, M. A., Dr. Min (Clinical)**  
Director, Christian Counselling Centre  
Chairperson, Ethics Committee

**Dr. Alfred Job Daniel, D Ortho MS Ortho DNB Ortho**  
Chairperson, Research Committee & Principal

**Dr. Nihal Thomas**  
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)  
Secretary, Ethics Committee, IRB  
Additional Vice Principal (Research)

A sum of Rs. 40,000/- (Rupees Forty Thousand only) will be granted for First years and for the Second years the rest 40,000/- (Rupees Forty Thousand only) will be granted. Total of Rs. 80,000/- (Rupees Eighty Thousand only) will be granted for Two years.

Yours sincerely

**Dr. Nihal Thomas**  
Secretary (Ethics Committee)  
Institutional Review Board

**Dr Nihal Thomas**  
MBBS MD MNAMS DNB (Endo) FRACP(Endo) FRCP(Edin)  
Secretary (Ethics Committee)  
Institutional Review Board

CC: Dr. Reginald Alex, Department of General Medicine, CMC

# PLAGIARISM CHECK CERTIFICATE

The screenshot shows a Turnitin class homepage in a Safari browser. The browser's address bar displays the URL: [https://turnitin.com/s\\_class\\_portfolio.asp?r=51.276066898135&svr=3&lang=en\\_us&aid=80345&cid=8539677#](https://turnitin.com/s_class_portfolio.asp?r=51.276066898135&svr=3&lang=en_us&aid=80345&cid=8539677#). The page title is "Turnitin".

Navigation tabs include: Class Portfolio (selected), Peer Review, My Grades, Discussion, and Calendar.

Now viewing: HOME > THE TAMIL NADU DR.M.G.R.MEDICAL UTY 2014-15 EXAMINATIONS

Welcome to your new class homepage! From the class homepage you can see all your assignments for your class, view additional assignment information, submit your work, and access feedback for your papers. Hover on any item in the class homepage for more information.

**Class Homepage**

This is your class homepage. To submit to an assignment click on the "Submit" button to the right of the assignment name. If the Submit button is grayed out, no submissions can be made to the assignment. If resubmissions are allowed the submit button will read "Resubmit" after you make your first submission to the assignment. To view the paper you have submitted, click the "View" button. Once the assignment's post date has passed, you will also be able to view the feedback left on your paper by clicking the "View" button.

Assignment Inbox: The Tamil Nadu Dr.M.G.R.Medical Uty 2014-15 Examinations

Info	Dates	Similarity	
TNMGRMU EXAMINATIONS ⓘ	Start 01-Sep-2014 11:27AM Due 15-Aug-2015 11:59PM Post 15-Aug-2015 12:00AM	4%	<a href="#">Resubmit</a> <a href="#">View</a>

4%

Copyright © 1998 – 2014 iParadigms, LLC. All rights reserved.  
[Usage Policy](#) [Privacy Pledge](#) [Helpdesk](#) [Research Resources](#)

## CONTENTS

<u>Title</u>	<u>Page number</u>
<b>Introduction</b>	14
<b>Aims and objectives</b>	16
<b>Literature review</b>	17
<i>The biology of Rickettsial disease</i>	18
<i>Scrub typhus</i>	21
<i>Epidemiology</i>	26
<i>Risk factors</i>	29
<i>Pathogenesis</i>	32
<i>Clinical and laboratory manifestations</i>	36
<i>Diagnosis of scrub typhus</i>	40
<i>Differential diagnosis of scrub typhus</i>	42
<i>Complications of scrub typhus</i>	44
<i>Prevention and control of scrub typhus</i>	46
<i>Antinuclear antibodies</i>	48
<i>Antinuclear antibodies and infection</i>	54
<i>Justification of the study</i>	56

<b>Patients and Methods</b>	58
<b>Results</b>	
<i>Patient demographics</i>	69
<i>Clinical profile of patients</i>	71
<i>Prevalence and patterns of antinuclear antibodies in scrub typhus</i>	73
<i>Correlation of antinuclear antibodies with organ dysfunction</i>	80
<i>Antinuclear antibodies and duration of hospital and ICU stay in scrub typhus</i>	90
<i>Antinuclear antibodies and mortality in scrub typhus</i>	93
<b>Discussion</b>	94
<i>Prevalence and patterns of antinuclear antibodies in patients with scrub typhus</i>	94
<i>Antinuclear antibodies and outcomes in scrub typhus</i>	96
<b>Limitations</b>	98
<b>Conclusions</b>	99
<b>Bibliography</b>	101
<b>Appendix</b>	109

ABSTRACT: Anti-nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus.

#### OBJECTIVES OF THE STUDY:

1. To estimate the prevalence of anti-nuclear antibody expression in Scrub typhus, in comparison to patients with other acute infective febrile illnesses.
2. To study the patterns of anti-nuclear antibodies expressed in Scrub typhus.
3. To study the influence of antinuclear auto-antibodies on organ dysfunction, hospitalisation and outcomes in Scrub typhus.
4. To study the predictive value of ANA in Scrub typhus.

#### METHODS:

This prospective, observational cohort study was conducted in the Department of General Medicine of a tertiary care hospital between January, 2013 and January, 2014. Adult patients hospitalised in the medical wards with an acute febrile illness (AFI), fulfilling the diagnostic criteria for Scrub typhus infection [89 cases] and other acute infective febrile illnesses [60 controls] were included in the study. After obtaining a written consent from patients fulfilling the inclusion criteria, the necessary demographic data and the data regarding the current illness and investigations were collected. Patients and controls were tested for the presence of antinuclear antibodies immediately after admission. Severity of the illness was measured using scoring systems such as APACHE III and SOFA and its correlation with ANA positivity was studied. Patients were also assessed for complications of scrub typhus along with need for ventilation and use of vasoactive agents. Duration of hospital stay, duration of ICU stay and hospital outcomes were assessed along with their correlation to ANA positivity. Patients with antinuclear antibodies were followed up after a period of 6 weeks and repeat ANA testing was done. Descriptive and bivariate analysis was done.

## RESULTS:

89 cases of scrub typhus and 60 controls with other acute infective febrile illnesses were included in the study. The prevalence of antinuclear antibodies was 53.93% in scrub typhus patients and 15% in patients with other acute febrile illnesses ( $p < 0.01$ ). On testing after a period of 6 weeks, antinuclear antibodies persisted to be present in 15.6% patients with scrub typhus. The speckled pattern of antinuclear antibodies was most commonly seen (93.75%). On bivariate analysis, the APACHE III scores and antinuclear antibody positivity showed correlation which was tending towards statistical significance. [OR-1.01,  $p=0.07$ ]. There was also a positive correlation with antinuclear antibodies in scrub typhus and the development of acute respiratory distress syndrome [OR-2.44,  $p=0.04$ ], central nervous system manifestations [OR-6.65,  $p=0.08$ ] and liver dysfunction [OR-2.25,  $p=0.06$ ]. However, no correlation was found between the presence of antinuclear antibodies and SOFA scores, duration of hospital stay, duration of ICU stay and mortality in scrub typhus.

## CONCLUSIONS:

Antinuclear antibodies were found in a significant proportion of patients with scrub typhus and the speckled pattern was commonly expressed. This appears to be related to the acute phase of illness and these antibodies showed a positive correlation with severity of illness as assessed by the APACHE III scoring system, respiratory, neurological and hepatic manifestations. Presence of these antibodies showed no correlation with duration of hospital stay and ICU stay. Further studies are needed for better understanding of this phenomenon.

## **INTRODUCTION**

Scrub typhus is a zoonotic disease. *Orientia tsutsugamushi*, the causative organism of Scrub typhus, is a Gram-negative, obligate intracellular parasite. The organism is transmitted to humans by the bite of the larval form(chigger) of the trombiculid mite, *Leptotrombidium* species.(1)

Infection results in an acute febrile illness. This illness is endemic to South East Asia, the Asia-Pacific region and northern Australia, also called the Tsutsugamushi triangle.(2) The pathophysiology is that of a focal and disseminated vasculitis which results in its protean manifestations. Proliferation of the organism in the endothelium of small blood vessels results in endothelial disruption which causes fluid leak, platelet aggregation and neutrophil proliferation. This leads to microinfarctions, secondary to the focal occlusive angiitis.(3)

Commonly seen during the cooler months, Scrub typhus constitutes 47.5% of the cases of acute undifferentiated febrile illness in South India.(4) Course of illness can vary from a simple febrile illness with early defervescence to a devastating disease with multisystem involvement and significant morbidity and mortality. It has a high case fatality rate, although recent studies have depicted a downward trend in case fatality. (5,6)

Pathogenesis of this disease is poorly understood and factors affecting outcomes are not well studied. Unpublished data from the ICU of a tertiary care hospital in South India has detected the presence of antinuclear antibodies in the serum of patients who present with Scrub typhus. The reason for this is not clear and its effect on morbidity and mortality is not known. We postulate that patients who manifest multi organ dysfunction in severe Scrub typhus may have a nonspecific expression of this immunological marker. It would also be of prognostic significance to evaluate if the non-specific-



ic expression of this antibody is associated with a higher incidence of organ dysfunction and poorer outcomes. Further studies to understand this phenomenon are warranted

This prospective study was undertaken to evaluate the prevalence of ANA expression and patterns seen with relation to patients with Scrub typhus infection needing hospitalization. Antinuclear body expression was correlated with severity of illness, organ dysfunction and outcomes. Patients with other acute infective febrile illnesses were also assessed for ANA expression and outcomes, for comparison.

## **AIM**

To study the association between anti-nuclear antibody (ANA) expression and severity of illness, organ dysfunction and outcomes in Scrub typhus.

## **OBJECTIVES**

1. To estimate the prevalence of anti-nuclear antibody expression in Scrub typhus, in comparison to patients with acute infective febrile illnesses other than Scrub typhus.
2. To study the patterns of anti-nuclear antibody expressed in Scrub typhus.
3. To study the influence of antinuclear auto-antibodies on organ dysfunction, hospitalization and outcomes in Scrub typhus.
4. To study the predictive value of ANA in Scrub typhus.

## **REVIEW OF LITERATURE**

**THE BIOLOGY OF RICKETTSIAL DISEASE**

Rickettsial disease has existed throughout the world in endemic and enzootic foci. Historically, epidemics of louse borne typhus have resulted in more deaths than all the wars combined.(7) The earliest description of typhus was by Hippocrates in 460 B.C and subsequently historical records of Napoleon's army having to retreat from the war with Russia in 1812 due to his army being reduced 42 fold by typhus.(8) In recent years, there has been a re-emergence of rickettsial infections, more commonly reported in the tropics and amongst travellers.

Tropical Rickettsioses refers to a group of zoonotic infections caused by organisms of the family Rickettsiaceae, of the order, Rickettsiales. The family includes 3 tribes- Rickettsieae, Ehrlichieae and Wolbachieae. The tribe Rickettsieae has 3 genera- Rickettsia, Coxiella and Rochalimaea.(9) This classification system continues to be modified as newer bacteria are discovered. The genus Rickettsia has 3 groups- 1.) the typhus group(TG) which includes R.prowazekii, R.typhi and R.-canada; 2.) the spotted fever group(SFG) which has 20 species; 3.) the Scrub typhus group. More recently, studies have shown evolutionary unity of the typhus and spotted fever group, while Scrub typhus has been transferred to a new genus, Orientia. (1)(9) With the advent of 16S rRNA analysis for molecular taxonomy, there has been further reclassification.

These organisms are obligate intracellular gram negative coccobacilli that exist freely in the cytosol of infected arthropod hosts. They maintain intimate relations with their arthropod hosts on whom they are dependent for replication. Within the arthropod vectors, they multiply and are transmitted transovarially. The distribution of these invertebrate hosts is responsible for the extensive ecologic and geographic distribution of Rickettsial infections.(10)

Arthropod hosts include ticks, fleas, mites and lice. Transmission to humans and other vertebrate hosts occurs through salivary secretions or faeces of the infected vector.

Although many rickettsiae are pathogenic to humans, with the exception of *R. prowazekii*, the vertebrate host is not essential for the life cycle of the organism.

Human infection is accidental and often, a dead end. Though predominantly transmitted by the infected arthropod, the aerosol and blood transfusion route have also been described. (11)

The life cycle of Rickettsial organisms is closely related to the arthropod host. The arthropod serves as an effective vector, reservoir and amplifier in the rickettsial life cycle. Therefore, the geographical distribution and seasonal incidence of Rickettsioses parallels that of the arthropod vector.

## **SCRUB TYPHUS**

The organism causing scrub typhus was first described by the Japanese in the 1920. Hayashi proposed the name *Theileria tsutsugamushi* and thereafter, in 1930, Nagaya and his colleagues proposed *Rickettsia orientalis*. In 1995, the name *Orientia tsutsugamushi* was proposed in honour of the work of Hayashi and Nagaya.(1) They belong to the order, Rickettsiales, family, Rickettsiaceae and tribe Rickettsiae. This is the only organism to be classified under the genus *Orientia*. *Orientia tsutsugamushi* has exclusively been described in the eastern hemisphere.(9)

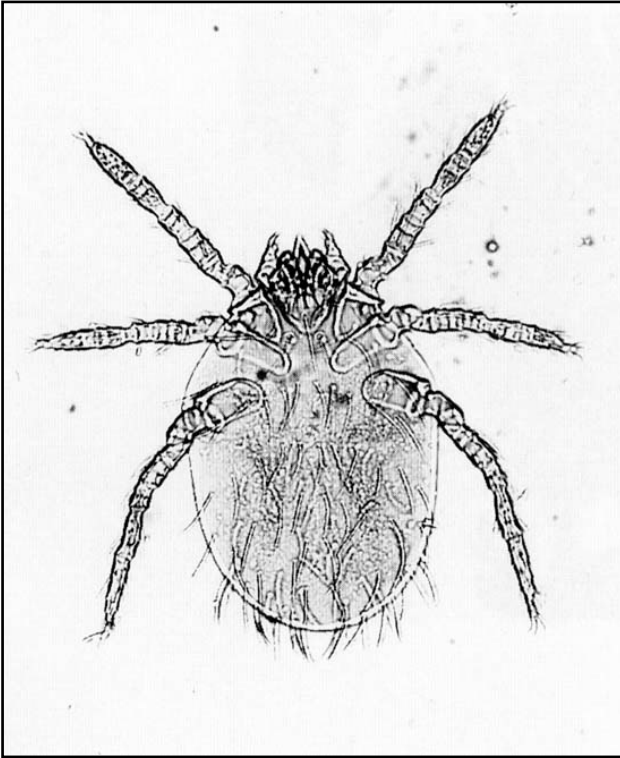
Members of this species are rods, 1- 3  $\mu\text{m}$  in length and 0.5-0.8  $\mu\text{m}$  in diameter. They are obligate, intracellular gram negative parasites. The most striking feature differentiating this organism from other species in the genus *Rickettsia* is that the outer leaflet of the cell wall is thicker than the inner. The opposite is true for other *Rickettsia* species. The other differentiating feature is the absence of peptidoglycan and lipopolysaccharide in *Orientia tsutsugamushi*, making the organism soft and fragile. Muramic acid, glucosamine and hydroxyl fatty acids are absent in the cell wall. The growth of this organism is also found to be more resistant to Penicillin. The major protein on the cell wall is the 56 kDa protein.(1)

*O. tsutsugamushi* can be cultivated on the yolk sacs of developing chick embryos. It can also be cultured on HeLa, Vero and BHK cell lines. The organisms exhibit intracellular growth with a predilection for the perinuclear cytoplasm. Release from the host cytoplasm is achieved by a budding process. A doubling time of 9- 18 hours has been described.

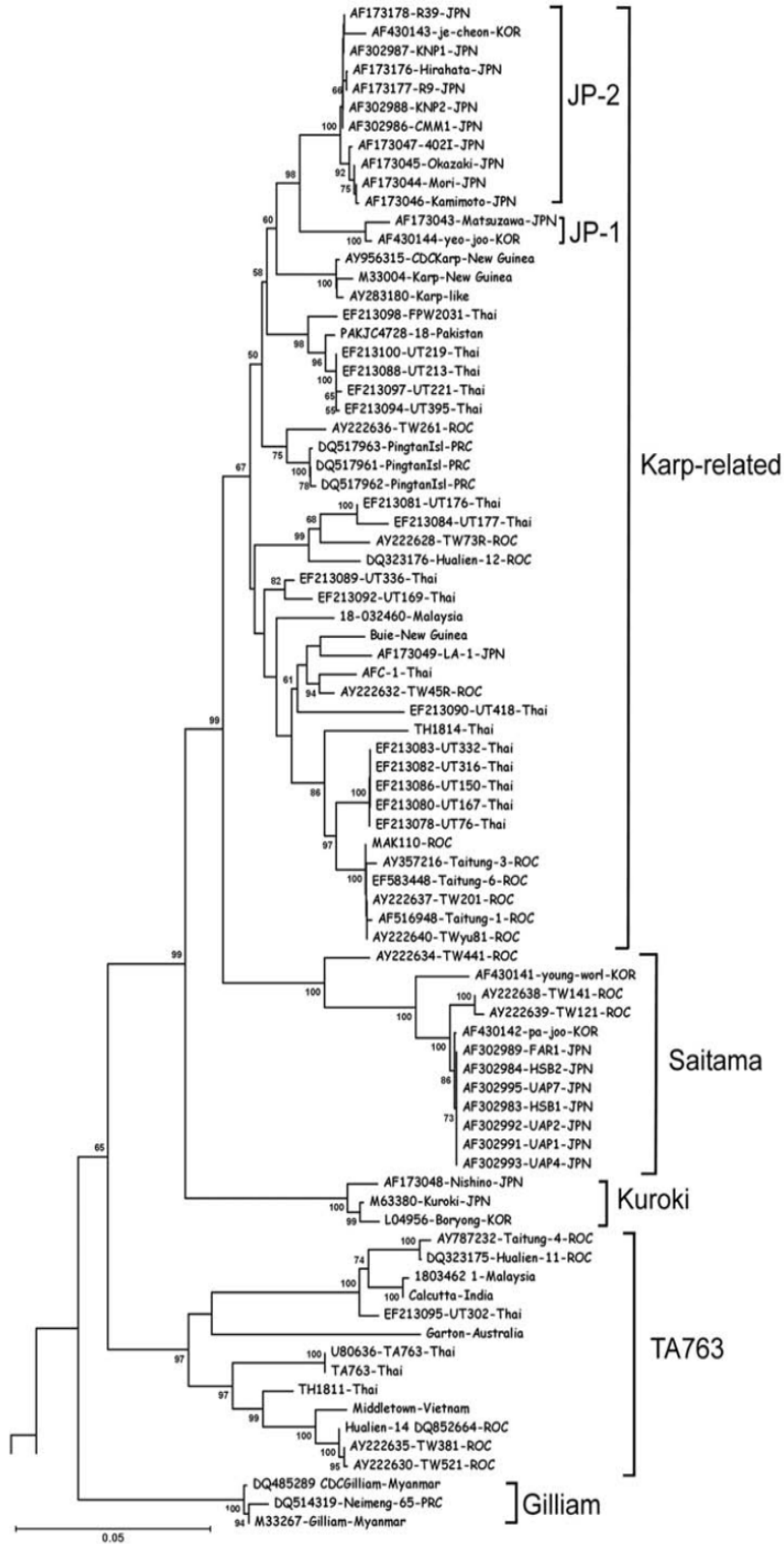
More than 20 antigenic variants and strains have been described such as Karp, Gilliam, Kato, Shimokoshi, Kawasaki and others, on the basis of antigenic differences in the 56 kDa protein on the cell surface. They also differ in their virulence to mice. Of these, the Karp strain is most endemic to South Asia.(5)

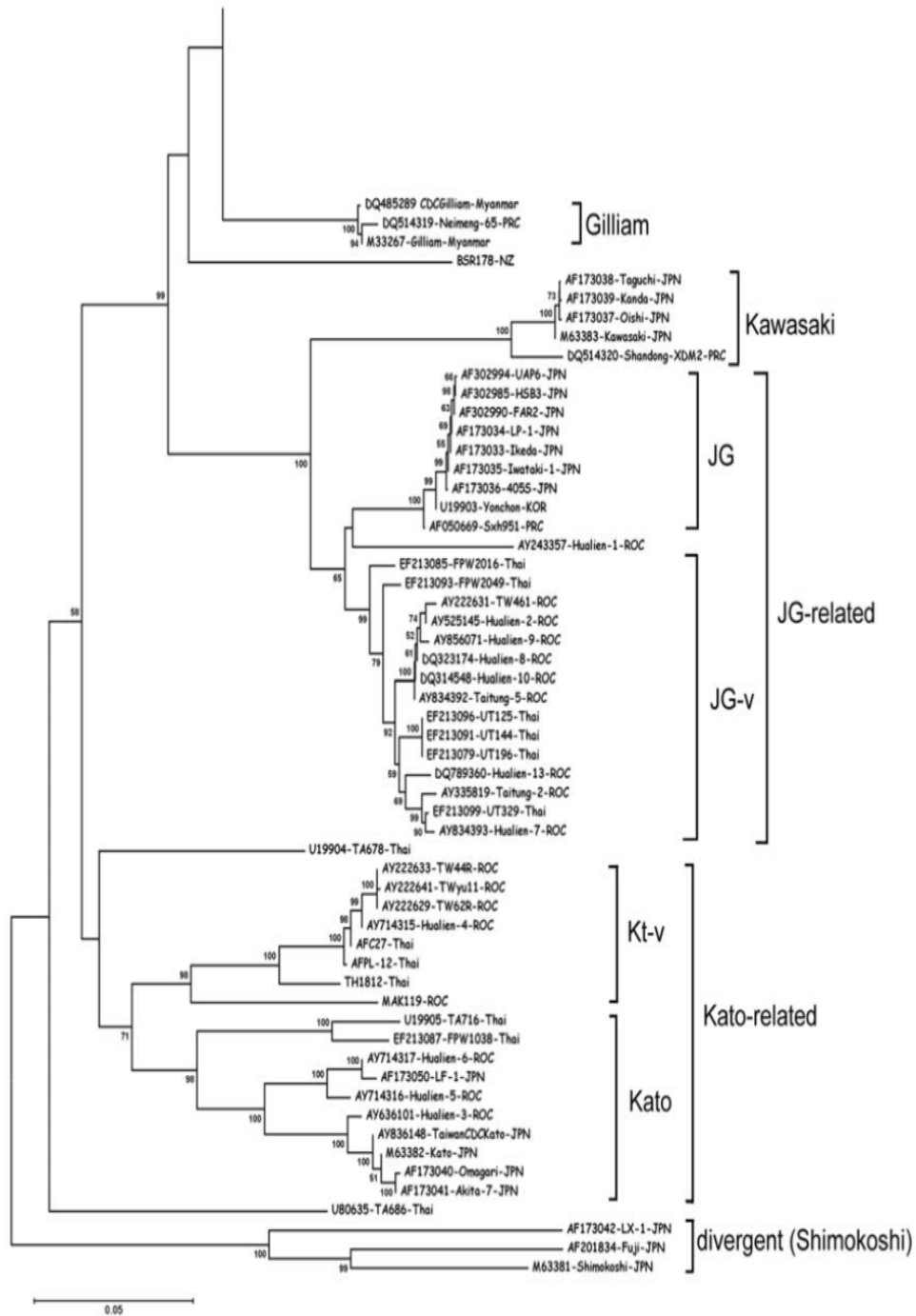


Infection is transmitted to humans and other vertebrates by mites. The organism multiplies within mites of the *Leptotrombidium* genus and is maintained in the environment by vertical or transovarial transmission. Trombiculid mites typically feed on wild rats. Humans get infected by the bites of chiggers or the larval forms of the trombiculid mite. (6)



**Figure 1: *Leptotrombidium deliense*, the primary vector of scrub typhus**





**Figure 2: The phylogenetic tree of *Orientia tsutsugamushi*. Cell surface antigen 56kDa is the basis for this classification**

## **EPIDEMIOLOGY**

Scrub typhus occurs in the eastern hemisphere. It is endemic to the 'tsutsugamushi triangle' formed by south and southeastern Asia, northern Australia and the Asia-Pacific rim.(2) This disease is typically seen in a rural or semi urban environment.(12) One million patients are affected annually and one billion people are at risk of this infection.(13)

The microbe has been found to cause disease in a geographically diverse environment ranging from mountainous regions to tropical foL

?LKrests covering a 13,000,000-km<sup>2</sup> area. The organism too depicts a high degree of genotypic and diversity. The major factors that influence efforts to characterize antigenic subtypes appear to be the economic and political environment of the region, along with impact of the disease. A mortality rate of ~60% was described in the pre-antibiotic era. However, recent studies have shown a downward mortality trend.

In India, the earliest records of scrub typhus are from 1917 where a typhus-like fever was described. The illness occurs in sporadic seasonal outbreaks commonly seen in the cooler months of August to October. The primary vector is *L.deliense*. Infection has been reported from Northern and Southern India.(14) An outbreak was described in Tamil Nadu in October, 2002 and subsequently this illness has been reported more frequently. (15) In some regions Scrub typhus constitutes upto 50 % of the hospitalizations for acute febrile illness.

Though the disease is being more promptly diagnosed in indigenous populations and endemic regions, diagnosis can often be a challenge, especially in the light of ecotourism and military operations. Delay in diagnosis and treatment can adversely affect prognosis and outcomes. (2)

Scrub typhus was associated with high mortality of close to 60 % previously. However with the advent of effective antibiotic therapy, a downward trend has been noted. A recent study done in South India has reported a case fatality of 9 %.(6)



**Figure 3: The 'tsutsugamushi triangle', endemic for scrub typhus**

## **RISK FACTORS**

In endemic areas, Scrub typhus is commonly associated with agricultural exposure. Human to human transmission is not known and various vector-related factors increase the risk of acquiring infection. These include environmental and behavioural factors.(12) Understanding the same is crucial to preventive and control strategies.

Infection is commonly seen in rural or semi urban environment. (16) Outdoor activities in moist and humid environments put individuals at risk for infection. Farmers and forest workers are at risk and activities such as field work, harvesting and wood and weed gathering have a positive association. (17,18) Working in vegetable fields or woodland and hilly areas has been associated with risk of infection. Increased duration of sunshine, temperature and rainfall are positively associated with infection. (19)

Living at the edge of a village or closer to farmland or grassland puts individuals at risk of exposure to the chiggers. Presence of a yard around the house or the practice of piling weeds indoors is also positively associated. (20)

Studies have shown that men are more predisposed to infection and this may be attributed to occupational trends. Behavioral risk factors include tendency to rest in direct contact with grass, use of clothing that increases exposure of skin to vegetation while working, lack of use of insect repellants and a failure to wash self or change/ dust clothes after returning from the fields. (20) Open defecation and urination and direct contact of skin with scrub vegetation predisposes to infection.(16)

A study done in India has highlighted several risk factors. Environmental exposures include bushes, wood, fodder, domestic animals and rodents. Use of protective equipment such as aprons, boots and long sleeved shirts decreased risk, as also the use of insect repellants. (21) Bathing after work and change of clothing lowers the risk of infection.



Health education measures have been shown to decrease risk of infection. Education regarding change of clothing, avoidance of direct contact of skin to grass and use to repellants has been shown to decrease the incidence of infection. (16,22)

Risk factors associated with a fatal outcome include the absence of an eschar, higher APACHE scores and admission to an intensive care unit. Delay in initiation of appropriate treatment increases the risk of adverse outcomes. (12,23)

## **PATHOGENESIS**

Scrub typhus is a zoonosis and the primary host of *Orientia* is the trombiculid mite. The organism multiplies and is maintained by the the arthropod host by transovarial transmission. Human infection is accidental and occurs when the chigger bites the human host and transfer of saliva containing the pathogen occurs. The organism multiplies at the site of inoculation and thereafter disseminates within the host. (3) Severity of infection is dependent on the virulence of the strain as well as host immunity.

The principle site of involvement is the endothelial cell. The pathogen invades the phagocytes and endothelial cells. A vasculopathy ensues. The pathogenic effects are caused by disruption of the adherens junctions between infected endothelial cells. This results in increased microvascular permeability with subsequent leakage of fluid. (24) This vasculopathy can affect any organ ranging from skin to the central nervous system resulting in the protean manifestations of this disease.

*Orientia* present in the saliva of the infected chigger gets inoculated and goes on to infect the dendritic cells and macrophages of the underlying dermis. The organism spreads lymphatogenously to the nodes draining the site of the eschar. This is evidenced by early development of lymphadenopathy in Scrub typhus. Subsequently, there is dissemination via the hematogenous route. A predominant involvement of the endothelial cells is seen along with macrophage involvement. These cells release cell-specific adhesion molecules.(25)

Host fibronectin interactions with the 56kDa type specific outer membrane protein of *Orientia* occurs.(26) Entry into the host cell occurs via interactions with the integrin,  $\alpha 5\beta 1$ . Signaling molecules, RhoA GTPase, Src kinase and FAK (focal adhesion kinase) are activated in response to the external stimulus. Talin and paxillin which are signaling adaptors get recruited to the infection site.

Actin reorganization and membrane ruffling occurs within 10 minutes of attachment. The organism is phagocytosed and forms a phagosome within the endothelial cell or macrophage.(27)

Inflammation in the dermis is initiated by the *Orientia* infected cells. The activated dendritic cells secrete inflammatory cytokines such as TNF  $\alpha$ , IL-6, IL-13  $\beta$ , MIP 1  $\alpha/\beta$ , MIP-2 and MCP-1. This results in the recruitment of leucocytes to the site of inflammation. (28) Chemokines of the CC subfamily, ie, MIP 1  $\alpha/\beta$ , MCP-1 and RANTES attract lymphocytes and monocytes. Those of the CXC subfamily, ie MIP-2, IL-8 attract neutrophils. Stimulation of the T cells by MIP 1  $\alpha/\beta$  and RANTES results in a Th1 response and IFN  $\gamma$  production while MCP-1 stimulation results in a Th2 response with IL-4 production. (27)

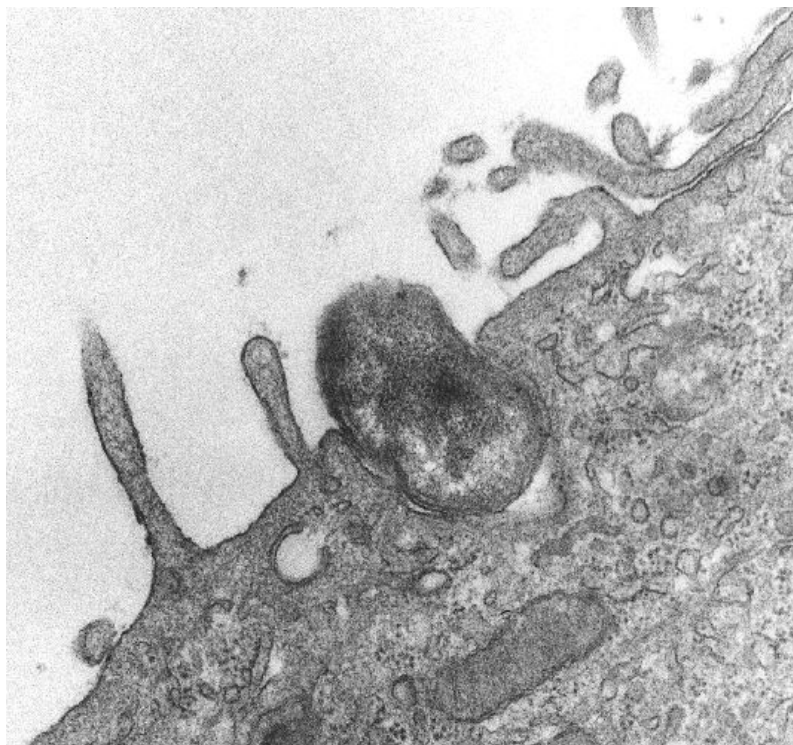
Endothelial cells are stimulated by the cytokines TNF- $\alpha$  and IL-1. This causes adhesion molecule up-regulation. ICAM-1, VCAM-1, P-selectin and E-selectin molecules promote cellular influx and further cytokine production. All of this results in a propagated local inflammatory response. Studies have shown that E-selectin levels in serum correlate with disease symptoms. (29)

Although inflammation and pathogenesis is mediated via inflammatory cytokines, the organism also ensures survival by evasion of the immune system.(30) A Th1 cellular response with production of INF- $\gamma$  is essential for containing infection while a Th2 response is often detrimental. However mouse models have demonstrated the presence of suppressive and activating cytokines of both types of cellular responses, highlighting the absence of a well polarized immune response. IL-12 stimulates T cells and natural killer cells towards a Th1 response and production of INF- $\gamma$  while IL-10 inhibits this and promotes a Th-2 response. INF- $\gamma$ , in a similar fashion inhibits a Th2 response. Severe and life threatening complications are known to occur with scrub typhus and this may be related to the suppression of TNF- $\alpha$  and IL-6 via IL-10. This imbalance, ie, low TNF- $\alpha$  and high IL-10 levels is associated with worsening condition of patients with bacterial infections.

A recent study has suggested that TNF- $\alpha$  levels can predict severity of scrub typhus in the acute infectious phase. (31) Systemic release of multiple pro-inflammatory cytokines in an unregulated fashion has been postulated to result in SIRS.

The role of humoral immunity in the pathogenesis of infection is not clearly understood. Antibodies may enhance phagocytosis of the infected cells by macrophages and polymorphonuclear cells. It may also prevent *Orientia* attachment, entry and replication in endothelial cells.(27)

Immunity to infection has been complicated by the antigenic diversity and the weak cross protection among various strains. Homologous immune protection by antibodies to the 56 kDa surface protein too wears off after a few years. Although profound antigenic heterogeneity deters the development of a whole cell vaccine, the common 56 kDa surface protein among various strains is being explored as a candidate for recombinant vaccine and research is underway.(27)



**Figure 4: The organism, *Orientia tsutsugamushi* being phagocytosed by a macrophage**

**CLINICAL AND LABORATORY MANIFESTATIONS**

The clinical presentation of scrub typhus can be varied. Some of the clinical features are non-specific.

Fever is the most common presenting symptom. It is reported by upto 98 % of patients. (32) It is of insidious onset and may be associated with non specific symptoms such as headache, myalgia, malaise and vomiting.(5) The mean duration of fever is  $9\pm 3$  days. (33)

An eschar may be found at the site of inoculation of the chigger. The appearance is that of a central necrotic, black crusted lesion with an erythematous halo resembling a cigarette burn. The prevalence of eschars have been reported in a very variable percentage of 10- 92%. (34) Eschars are commonly found over the chest, abdomen and hidden areas such as the axillae, groin, inframammary region and along the flexures. (35) They can provide a valuable clue to the diagnosis of scrub typhus.

Leucocytosis( $>11,500$  cells/ $\text{mm}^3$ ) is present in 30% of patients and upto 70% patients have evidence of thrombocytopenia( $<1,50,000$  cells/ $\text{mm}^3$ ). (5) Liver and renal function abnormalities are commonly seen.

Scrub typhus can affect virtually any organ system in the body and disease manifestations are protean.

### **Respiratory manifestations:**

Pulmonary symptoms are present in 60- 72% patients.(36) Breathing difficulty and cough are the common symptoms with or without chest infiltrates. Involvement can range from bronchitis, interstitial pneumonia to severe acute respiratory distress syndrome necessitating mechanical ventilation. (37)

ARDS is a dreaded respiratory complication and occurs in 11- 44% patients.(33,38) Histopathological evaluation has shown the vasculitis and diffuse alveolar damage.(39) Upto one-third of patients require mechanical ventilation.(33) Predictors of ARDS include hypoalbuminemia, delay in initiation of antibiotics and older age group.(38) ARDS is also associated with a high mortality rate.

Chest radiograph abnormalities are present in 50% patients in the first week of presentation. Common findings are bilateral reticulo-nodular opacities, alveolar shadows and ARDS pattern. Pleural effusions, hilar adenopathy, pulmonary oedema and septal lines may also be observed. (36,37)

### **Cardiac manifestations:**

Though an uncommon presentation, patients may present with features of myocarditis, cardiogenic shock and pulmonary oedema. Non specific changes on ECG and rhythm abnormalities have also been reported.(40–42) Symptoms are reported to completely resolve following treatment.

### **Hepatobiliary and gastrointestinal manifestations:**

Abdominal pain, vomiting and loose stools are common presenting symptoms. Hepatomegaly and splenomegaly are frequently found. GI vasculitis is the pathological process and upper GI bleeding has also been reported. Findings on endoscopy are that of mucosal bleeds, erosions and ulcers. (43,44)

Elevation of transaminases and alkaline phosphatase is seen in 70-80% patients.(33,45) A smaller percentage of patients have bilirubin elevation. Studies have demonstrated the presence of *Orientia* in the Kupffer cells of the liver.(28) The organism has a predilection for the hepatic sinusoidal cells, infiltrating the same and causes cholestasis and vasculitis in the portal area.(45)



**Renal involvement:**

Acute kidney injury has been reported in 40-53% of patients with scrub typhus.(46,47) Dysfunction can occur secondary to systemic vasculitis, hypoperfusion of the kidneys in shock, direct invasion of tubules causing acute tubular necrosis, rhabdomyolysis or interstitial nephritis secondary to NSAID or antibiotic use.(46) Renal failure is also a definite risk factor for mortality.(5)

Metabolic acidosis and elevated serum Creatinine levels have been associated with a poor prognosis.(5)

**Central nervous system manifestations:**

Headache is a common presenting symptom and is reported by 40 % of patients.(33) Upto 24 % patients may present with altered sensorium and 6% with seizures. Aseptic meningitis and meningoencephalitis are common manifestations.(48,49) Other manifestations include cerebrovascular injury, Guillain-Barre syndrome, movement disorders, plexopathy, neuropathy and acute disseminated encephalomyelitis. The underlying pathology is that of a vasculitis with central nervous system involvement.(50–54) CSF studies show a lymphocytic pleocytosis with negative CSF cultures.

## **DIAGNOSIS**

Scrub typhus often presents as an acute undifferentiated febrile illness that is difficult to distinguish from Dengue, Malaria, Leptospirosis and Enteric fever. An eschar may provide a valuable clue but is present in a highly variable percentage. An eschar can also be present in other rickettsial fevers and cutaneous anthrax. Serology is hence the mainstay of diagnostics.(55)

Indirect immunofluorescence assay(IFA) is the current gold standard diagnostic test. Antibodies in the patient's serum, bound to scrub typhus antigen is detected by fluorescent anti-human antibody. (56) A four-fold dynamic rise in titers in paired sera is considered diagnostic. However, the demonstration of a rise in titers would impede early initiation of antibiotics. Hence, a single acute serum cut-off antibody titer is considered diagnostic, for convenience. Studies have show that cut-offs range from 1:10 to 1:400.(56)

There are several limitations to using a single acute serum antibody cut-off for diagnosis. Cut offs should be based on antibody titers of the local healthy population. This is important to distinguish background immunity from true infection, especially in areas endemic for scrub typhus. A lower cut-off should be used for individuals travelling to endemic areas. The antigens used in the IFA are Karp, Gilliam and Kato even though the antigenic heterogeneity of Scrub typhus is well known.(57) Organism isolation and culture has proven to be time consuming and labour intensive. The median time to positivity is 27 days and hence it is not useful for routine diagnosis. (56)

Research is focused on PCR studies of eschars and blood to detect the presence of *Orientia* DNA or antigen. This method, though accurate, would be expensive.(25)

## **DIFFERENTIAL DIAGNOSIS OF SCRUB TYPHUS**

Many of the causes for acute febrile illness in the tropics can closely mimic scrub typhus. These infections should be considered in the differential diagnosis of scrub typhus. Malaria may have a presentation similar to scrub typhus and diagnosis is based on peripheral blood smear and other rapid diagnostic tests. Arbovirus infections such as Dengue and Chikungunya, Leptospirosis, Infectious mononucleosis and HIV are other differentials for scrub typhus. Non infectious causes of vasculitis also need to be considered.

Although serology is a valuable tool in differentiating scrub typhus from other causes, rapid defervescence of fever with the use of appropriate antimicrobial therapy also aids in confirmation of diagnosis.

## **COMPLICATIONS OF SCRUB TYPHUS**

Severity of illness is dependent on the infecting strain, host factors and time to diagnosis and treatment. Scrub typhus is associated with myriad complications due to the systemic vasculitis. Any organ system may be involved and a delay in diagnosis and treatment has been associated with an increased incidence in complications and mortality related to the disease. Complications of scrub typhus include:

- Lung injury and Acute respiratory distress syndrome
- Acute kidney injury
- Central nervous system complications such as aseptic meningitis and seizures
- Hepatitis, pancreatitis and gastrointestinal vasculitic ulcers
- Myocarditis with shock
- Hematological complications such as hemophagocytosis
- Sepsis with MODS and septic shock.

Previous studies on scrub typhus reported a high mortality rate of 60% secondary to multi organ dysfunction. However, recent studies have demonstrated a decreasing mortality trend with a more recent study reporting a case fatality rate of 9%.

## **TREATMENT OF SCRUB TYPHUS**



The first drug to be used in the treatment of Scrub typhus was Chloramphenicol and reports of the use of this drug date back to the 1940s. However, due to the issues of bone marrow suppression and aplastic anaemia, this drug has been used less frequently in the recent years. Tetracyclines are the mainstay of treatment and are the most commonly used drugs in treatment of scrub typhus. Studies have compared the efficacy of single dose versus a one week course of Doxycycline. The use of Doxycycline is associated with gastrointestinal side effects and Tetracycline use is contraindicated in pregnancy due to teratogenicity and use in young children has been associated with staining of the teeth. Macrolides such as Azithromycin were later introduced in the treatment of scrub typhus. Advantages include a shorter course of antibiotics with fewer gastrointestinal side effects. However, macrolide use has been associated with transient elevation of liver enzymes and the cost of Azithromycin is significantly higher than Doxycycline.

In recent years, Quinolones and Rifampicin have also been used in the treatment of this infection with good results. Quinolones such as Levofloxacin were found to be less efficacious in patients with multi-organ dysfunction and higher APACHE scores. Use of Rifampicin is also associated with multiple side effects and issues of spread of Rifampicin resistant tuberculosis has resulted in sparse use of this drug in the treatment of Rickettsial infection.

There has been an increased incidence of reports of Doxycycline resistance in northern Thailand. In such cases use of Azithromycin and Rifampicin is recommended. In patients with severe infection, parenteral therapy with Azithromycin has been found to be more effective than oral Doxycycline.

**PREVENTION AND CONTROL OF SCRUB TYPHUS**

**Prevention of infection-** Scrub typhus is a zoonotic disease. Infection can be prevented by taking precautionary measures especially during exposure to scrub vegetation and during the cooler months. Use of insecticide repellants and appropriate personal protective equipment such as socks and long sleeved clothing has been proven to be effective in preventing infection. Dusting of clothing and footwear and baths after visiting an endemic area can prevent infection. Control of rodent and marsupial reservoirs can prevent the vectors from entering areas where human beings live and work.

**Prophylaxis against scrub typhus-** Use of Doxycycline and Azithromycin once a week during and 6 weeks after exposure has been found to be effective in the prevention of scrub typhus.

Research is underway in the development of an effective vaccine for prevention of Scrub typhus. Hurdles in the development of a vaccine include a large range of genotypic variants and differences in geographical distribution of the various strains. Infection with one strain does not confer immunity to infection by another strain.

## **ANTINUCLEAR ANTIBODIES**

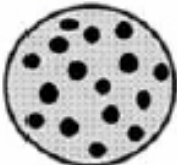



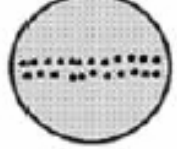
Antibodies to nuclear antigens are found in the serum of patients with systemic autoimmune disease. They were first described in the 1940s by Hargraves while studying the Lupus Erythematosus (LE) cell – phagocytosis of nuclei of disrupted cells was promoted by these autoantibodies. The LE cell is a phagocyte with an ingested nucleus. The LE cell test has been replaced in most laboratories by newer tests with greater sensitivity and specificity. The development of an Immuno-fluorescent assay (IFA) for detection of antinuclear antibodies has been a big milestone in immunology. Further sub-classification of antinuclear antibodies into individual, specific antigen-antibody reactions has been made possible by the use of purified nucleic acid antigen substrates.(58) Current immunological tests can detect 10-12 antigen-antibody specificities using recombinant or biochemically purified antigens. They are of great importance in the context of diagnostics and prognostication of rheumatologic conditions.

Although classically described in the setting of autoimmune disease, studies have shown that autoantibodies may also be detected in healthy individuals. (59) The prevalence of antinuclear antibodies in healthy individuals is 3-15%. These antibodies have also been found to occur in patients with chronic infections such as Hepatitis C, bacterial endocarditis, HIV infection, tuberculosis and lepromatous leprosy.(60) Drug induced lupus secondary to Procainamide, Hydralazine, Isoniazid, Penicillamine and anti-TNF-alpha therapy is also associated with positive antinuclear antibodies. (61) Antibodies are also found in greater frequency in women and with increasing age.

Indirect immunofluorescent test is considered as the most reliable screening test for antinuclear antibodies. Diluted human serum is placed on frozen mouse liver or kidney sections. Fluorescent conjugates of anti-human gamma globulin is used to detect the presence of autoantibody attached to the mouse antigen. Titers of antinuclear body are known to vary greatly.(58)

The ANA pattern is also of importance and four major patterns have been recognized: homogenous or solid, peripheral or rim, nucleolar and speckled patterns.

- The homogenous pattern is associated with connective tissue disease and drug induced lupus.
- The speckled pattern is seen in SLE, RA, Sjogren's syndrome and systemic sclerosis
- The peripheral rim pattern is seen in SLE and correlates with antibodies to dsDNA
- The nucleolar pattern is seen in scleroderma and to lesser extent in Sjogren's syndrome and SLE.(62)

ANA pattern	Antigen	Associated diseases
Speckled 	ENA, RNP, Sm, Ro/SSA, La/SSB, Scl-70, Jo-1, ribosomal-P	SLE, MCTD, Systemic sclerosis, Sjögren's syndrome, PM
Homogenous 	dsDNA, Histones	SLE, Drug-induced SLE
Peripheral (rim) 	RNP, Sm, Ro/SSA	SLE, Systemic sclerosis
Nucleolar 	Anti-PM-Scl, anti-RNA polymerase I-III, anti-U3- RNP, To RNP	Systemic sclerosis, PM
Centromere 	CENP A-E	Limited systemic sclerosis

ENA: Extractable nuclear antigens; RNP: Ribonucleoproteins; SLE: Systemic lupus erythematosus; MCTD: Mixed connective tissue disease; PM: Polymyositis; dsDNA: Double-stranded deoxyribonucleic acid; CENP: Centromere protein.

**Figure 5: Patterns of antinuclear antibodies and the associated diseases**

**ANTINUCLEAR ANTIBODIES AND INFECTION**



The pathogenic mechanism leading to the formation of autoantibodies is poorly understood.(63) Environmental triggers such as infections can trigger autoimmune diseases in genetically predisposed individuals. Studies have shown that living in an infectious environment from a young age favours the formation of autoantibodies. This may be attributed to molecular mimicry between the nuclear components of infectious agents and normal cells. However, they do not predict development of lupus.(64)

Non autoimmune patients have demonstrated presence of autoantibodies during acute bacterial, viral, parasitic and rickettsial infections such as ANA, ASCA, LA, etc.(60) Autoantibodies have also been found with greater frequency in patients with tropical infections and chronic diseases such as tuberculosis, leishmaniasis, leprosy and Hepatitis B and C. The most common pattern is the speckled type. This may represent neutrophil activation or molecular mimicry rather than true autoimmune disease. The absence of demonstrable antibodies to DNA or extractable nuclear antigens suggests that this may be a non-specific manifestation of immune system activation. An article studying the same has recommended caution in the interpretation of auto-antibody tests in persons with tropical infections and subjects from the tropics.(65)

Autoantibody production has been studied in considerable detail in patients with malaria since the 70s. Recent immunofluorescence studies have demonstrated the presence of cytoplasmic diffuse, nuclear speckled fluorescent patterns of antinuclear antibodies in chronic malaria. This expression can suggest molecular mimicry or polyclonal antibody stimulation resulting in antibodies directed at self-targets. The study has also suggested use of immunofluorescent studies for early detection of disease, hence aiding early treatment.(66)

**SCRUB TYPHUS AND AUTOANTIBODY PRODUCTION**

**JUSTIFICATION OF THE STUDY**

Clinical manifestations of scrub typhus are a result of vasculitis caused by infection. Anti-nuclear antibody expression has been observed in Scrub typhus and it is likely that it is a non specific expression, as can occur in 10 percent of patients in the absence of an autoimmune disease. In a pilot study of 40 patients with severe scrub typhus infection admitted to the intensive care unit, 16 (40%) were tested positive for ANA. We postulated that patients who manifest multi-organ dysfunction in severe Scrub typhus may have a nonspecific expression of this immunological marker. For prognostic significance, we evaluated if the expression of this antibody was associated with a higher incidence of organ dysfunction and poorer outcomes in scrub typhus.

This prospective study was undertaken to evaluate the prevalence of ANA expression and patterns seen with relation to patients with Scrub typhus infection needing hospitalization. ANA expression was correlated with severity of illness at presentation as assessed by the Sequential Organ Failure Assessment (SOFA) as well as the Acute Physiology and Chronic Health Evaluation (APACHE) III scores. In addition, ANA positivity was correlated with organ dysfunction and outcome.

Patients admitted to hospital with a diagnosis of scrub typhus were evaluated. Data on demographics, organ dysfunction, organ support required and outcomes was collected in pre-constructed data abstraction form. ANA expression was correlated with severity of illness, organ dysfunction, length of stay and mortality. Patients with acute infective febrile illnesses other than Scrub typhus were similarly assessed for ANA expression, for comparison.

## **METHODOLOGY**

**Study type:** Analytical

**Study design:** Prospective, observational study

We used two methodologies in this study. In the estimation of prevalence of antinuclear bodies, we used a case control design where patients with other acute febrile illnesses were used as the control arm. For studying the correlation of antinuclear antibodies with outcomes in scrub typhus, a cohort design was employed.

**Setting:** This study was conducted in the Department of Medicine, Christian Medical College, Vellore. Christian Medical College is a 2500-bedded tertiary care hospital situated in Vellore in the state of Tamil Nadu, South India. Previous studies done in this hospital have shown that Scrub typhus constitutes 47 % of all acute febrile illnesses requiring admission.(4)

**Duration of study:** Patients were recruited from January, 2013 to January, 2014 for the study.

**Study population:** Adult patients hospitalised in the medical wards with an acute febrile illness(AFI), fulfilling the diagnostic criteria for Scrub typhus infection and other acute infective febrile illnesses(controls) were included in the study. After obtaining a written consent from patients fulfilling the inclusion criteria, the necessary demographic data and the data regarding the current illness and investigations were collected.

**Inclusion criteria- Cases**

1. Patients aged >16 years
2. Undifferentiated febrile illness of <21 days
3. Fulfilling diagnostic criteria for Scrub typhus infection
4. No other evident (focus of) infection following initial clinical evaluation

**Inclusion criteria- controls**

1. Patients aged >16 years
2. Acute febrile illness of <21 days
3. Not fulfilling diagnostic criteria for Scrub typhus
4. Matched for age and sex with the cases.

**Exclusion criteria**

1. Patients on immunosuppression
2. Patients with known underlying auto-immune disorders or malignancy
3. Patients who were on medications known to cause ANA positivity prior to the current illness, like sulphasalazine, Praziquantel, procainamide, isoniazid, hydralazine and certain anticonvulsants.
4. Patients unwilling to participate

**Withdrawal criteria**

1. Patients unwilling to continue participation in the study
2. Patients discharged against medical advice

**Sources of information**

1. Laboratory testing
2. Study participants or relatives
3. Hospital records

## **Outcome measures**

The following outcomes were planned and specifically assessed in this study

- Primary outcome-
  - o Estimation of the prevalence and patterns of antinuclear antibodies in Scrub typhus, in comparison to control groups.
  - o Correlation of antinuclear antibody positivity with organ dysfunction in scrub typhus, as assessed by the SOFA and APACHE III scoring systems
  
- Secondary outcomes-
  - o Duration of hospital stay in Scrub typhus categorized by ANA expression
  - o Duration of ICU stay in Scrub typhus categorized by ANA expression
  - o Deaths due to Scrub typhus infection categorized by ANA expression

## **Diagnostic criteria for Scrub typhus**

- AFI and the presence of a positive eschar and Scrub IgM ELISA, or;
  
- AFI plus a positive Scrub IgM ELISA plus defervescence within 48 hours of initiation of Doxycycline

Patients with a negative Scrub IgM ELISA who had an eschar were not included in the study.

We also looked at organ dysfunction in the study population.

- Myocarditis: clinically and pathologically defined as “inflammation of the myocardium” (*American Heart Association*); evidenced by ECG and ECHO changes and elevation of cardiac enzymes.
- Acute Respiratory distress syndrome(ARDS): acute lung injury of less than 1 week duration, with bilateral opacities on imaging, with no evidence of cardiac failure
  - mild ARDS: P/F ratio 201- 300 mmHg
  - moderate ARDS: P/F ratio 101- 200 mmHg
  - severe ARDS: P/F ratio  $\leq$  100 mmHg

(*Berlin, 2012, guidelines*)

- Acute kidney injury: Abrupt (within 48 h) reduction in kidney function defined as
  - an absolute increase in serum creatinine of 0.3 mg/dL or more ( $\geq 26.4 \mu\text{mol/L}$ ) **or**
  - A percentage increase in serum creatinine of 50% or more (1.5-fold from baseline) **or**
  - A reduction in urine output (documented oliguria of  $< 0.5 \text{ mL/kg/h}$  for  $>6 \text{ h}$ )

(*AKIN guidelines*)

- Aseptic meningitis: the clinical presentation and cerebrospinal fluid (CSF) findings that include lymphocyte-predominant pleocytosis of fewer than 500 cells/ $\mu\text{L}$ , normal glucose concentration, normal or slightly elevated protein, and negative bacterial antigen tests.



### Sample size calculation:

Unpublished data of research done in CMC had shown a 40% prevalence of ANA positivity in scrub typhus infection.

Prevalence of ANA positivity in other acute infective febrile illnesses was estimated at approximately 15%. (Studies done in Ghana on patients with malaria showed a 24 % positivity for ANA expression)

Sample size :

$$\text{“n” (each group)} = \frac{(p_0q_0 + p_1q_1) (z_{1-\alpha/2} + z_{1-\beta})^2}{(p_1 - p_0)^2}$$

Taking the prevalence of ANA expression in scrub typhus as 40% and prevalence in other acute febrile illnesses estimated at 15%, with an alpha error of 0.05 and a power of 80%, the number of patients required in each group was calculated to be 60.

In this study, we included 89 cases and 60 controls.

## **Methodology**

### ***Step 1: Recruitment***

Since this was a prospective study, all patients were recruited after an explanation of the study and the protocol. In the event that the patient was sedated or in an altered state of consciousness, consent was obtained from the nearest relative or guardian accompanying the patient (Annexure I). Scrub typhus and antinuclear antibody serologies were sent within 24 hours of admission in the hospital.

### ***Step 2: Data collection***

All consecutive patients admitted in the hospital medical wards fulfilling inclusion criteria were recruited. Data was collected in data abstraction forms (Annexure II).

The following data was collected specifically:

1. Baseline demographic data- Age, sex, occupation
2. History of co-morbidities such as diabetes, hypertension, coronary artery disease
3. History related to the acute febrile illness such as duration and associated symptoms
4. Examination findings
5. Laboratory parameters
6. Complications of the acute febrile illness- shock, acute respiratory distress syndrome, renal failure, myocarditis and aseptic meningitis
7. Scrub typhus serology
8. Anti-nuclear antibody serology

9. Laboratory variables necessary for computing serial SOFA scores on day 1, 3 and 5.
10. Laboratory variables necessary for computing APACHE III score at admission
11. Duration of ICU stay
12. Duration of hospital stay
13. Duration of mechanical ventilation and duration of vasoactive agent use.
14. Clinical outcomes

### **Laboratory assessment of Scrub typhus**

Serological diagnosis of scrub typhus was done by using the Immunoglobulin M enzyme linked immunosorbent assay, IgM ELISA, which utilises indirect immunofluorescence. This test uses the 56 kDA antigen. A conclusive diagnosis of scrub can be made only on the basis of a > four fold rise in titers in paired sera drawn at least 2 weeks apart. In the presence of adequate clinical evidence, a single sample may suffice.

### **Laboratory assessment of Antinuclear antibody**

Antinuclear antibodies in serum are detected by the principle of indirect immunofluorescence. This test utilises the Human epidermoid carcinoma cell line or the HEp-2 cells. These cells are fixed on slides with solvent and diluted human serum is added and incubated. The slides are washed and the cells are subsequently incubated with fluorescent antibodies to human immunoglobulins. Slides are examined using an ultraviolet microscope. After a In this study patterns of fluorescence such as homogenous, speckled, nuclear, etc can be studied. By adding saline and diluting the serum, the titer reading is determined. Serial dilutions are done to the patient's serum and the end point is when less than half of the cells on the slide show detectable fluorescence.

### ***Step 3: Statistical Analysis***

All study variables were described using descriptive statistical methods. Continuous variables which were summarized using mean and standard error.

The continuous variables were studied between the study and control groups and those with positive and absent ANA expression using two sample t-test or Mann-Whitney U test. Paired t- test was used for repeat samples of ANA.

Dichotomous variables were compared using chi-square or Fisher's exact test.

Bivariate analysis and logistic regression analysis was used to find correlation between ANA positivity and outcomes.

Data was entered and analyzed using SPSS software ( Statistical Package for Social Sciences, Version 20, IBM, New York , United States of America).

## **Funding**

The cost of the anti-nuclear antibody serology was borne by the institution through a grant allotted by the institutional review board for this specific purpose.

ANA serology was done at a cost of Rs. 490 per sample processed.

Scrub IgM ELISA was done at a cost of Rs. 725 per sample processed.

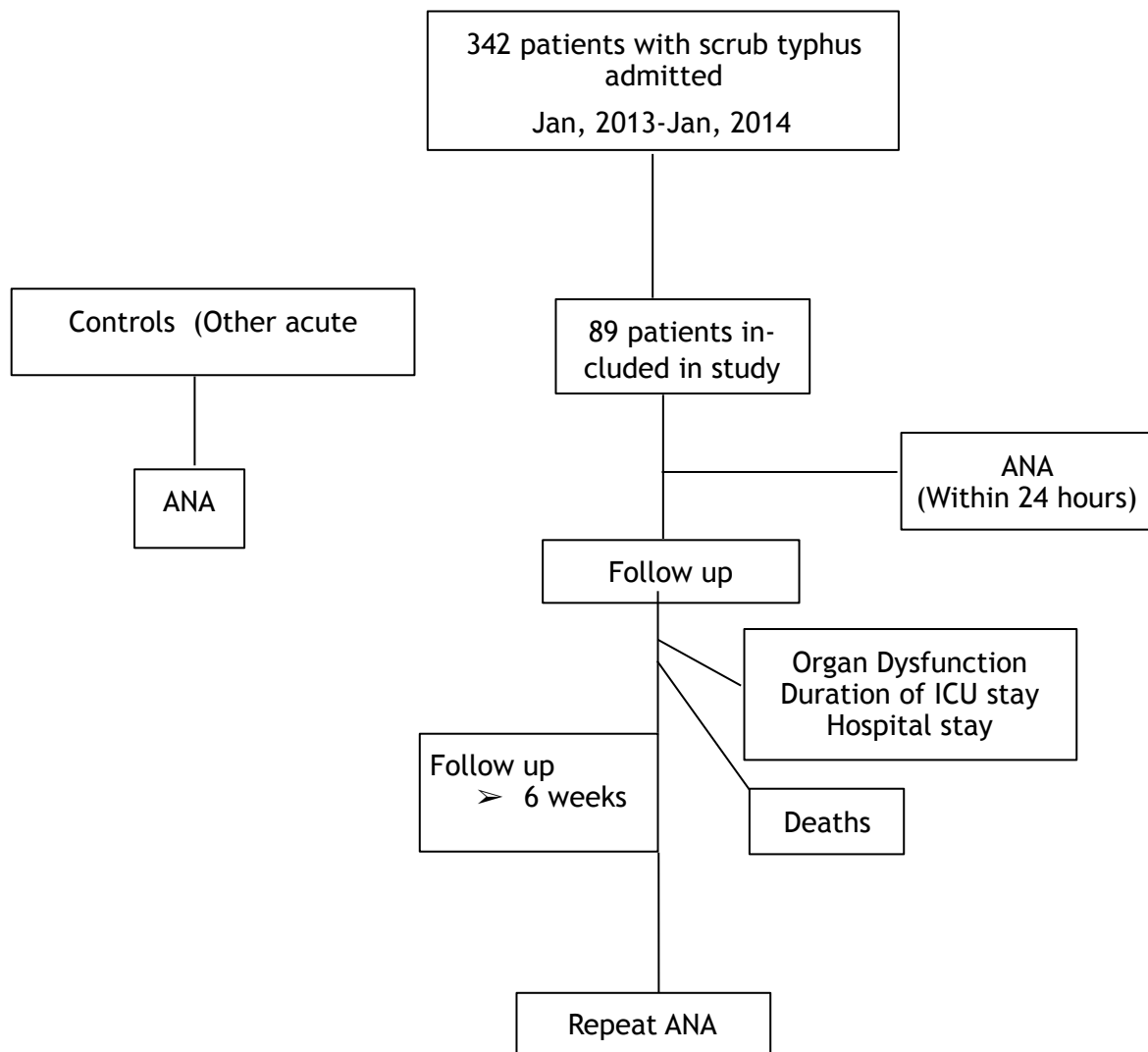
## **Institutional Research Board approval and ethical considerations:**

Consent was obtained at admission, before testing for anti-nuclear antibodies. Institutional Research Board (IRB) approval was obtained prior to commencement of the study.

Institutional ethics committee reviewed the study design and no major ethical concerns were raised.

## **RESULTS**

This prospective study was carried out in the Department of General Medicine, in-patient wing from January, 2013 to January, 2014. A total of 89 patients with Scrub typhus and 60 patients with other acute febrile illnesses were included in this study



**Figure 6: Strobe diagram of the progress through phases of the study**



## PATIENT DEMOGRAPHICS

**Table 1: Baseline characteristics of the study population**

	NUMBER	PERCENTAGE
<b>AGE (years)</b>		
16-30	15	16.9
31-50	37	41.6
51-70	24	27
>70	13	14.6
<i>Mean:</i> 46.48 <i>95% CI:</i> 43.16-50		
<b>GENDER</b>		
MALE	38	42.7
FEMALE	51	57.3
<b>OCCUPATION</b>		
Professional	2	2.2
Skilled	5	5.6
Unskilled	32	36
Unemployed	50	56.2
<b>LOCATION</b>		
Vellore	53	59.6
Chittoor	27	30.3
Other	9	10.1
<b>RISK/CO-MORBIDITY</b>		
Bronchial asthma	1	1.1
Diabetes mellitus	12	13.5
Diabetes, hypertension	2	2.2
HIV infection	2	2.2
Hypertension	13	14.6
Mental retardation	1	1.1
Pregnancy	3	3.4
Nil	55	61.8

The mean ( $\pm$ SD) age was 46.5 (16.9) with a range of 17-85 years. The number of male and female patients with scrub typhus was nearly equal though a slight female preponderance was observed, with a female to male ratio of 1.34:1. A significant proportion of patients were from Vellore (59.6%) and the other major area of residence was Chittoor, Andhra Pradesh (30.3%). Most patients were either engaged in unskilled work or unemployed.

## CLINICAL PROFILE OF PATIENTS WITH SCRUB TYPHUS

Fever was the most common presenting symptom and was present in all patients with a mean duration of 7.79 (95% CI 7.09-8.53) days. The other common presenting symptoms included myalgia (n=50) and breathlessness (n=49).

**Table 2: Profile of symptoms in scrub typhus patients recruited in the study (duration in days)**

	NUMBERS	MEAN (Days)		95% CI
<b>FEVER</b>	89	7.79	7.09-8.53	
<b>HEADACHE</b>	36	5.92	4.92-6.97	
<b>NAUSEA/VOMITING</b>	44	4.14	3.45-4.86	
<b>RASH</b>	2	4.5	4-5	
<b>COUGH</b>	22	4.32	3.36-5.23	
<b>ALTERED SENSORI- UM</b>	8	1.13	1-1.38	
<b>MYALGIA</b>	50	6.16	5.32-7.06	
<b>ABDOMINAL PAIN</b>	22	4.73	4.05-5.41	
<b>BREATHLESSNESS</b>	49	3.63	3.10-4.18	
<b>ARTHRALGIA</b>	6	4.33	3.33-5	
<b>JAUNDICE</b>	6	6.17	2.83-10	
<b>OLIGURIA</b>	7	1.71	1.14-2.43	

An eschar was noted in 75.3% (n=67) patients with scrub typhus, in this study. Tachycardia, defined as a heart rate above 100/min and tachypnea, defined as a respiratory rate above 24/min, was present in 80.9%(n=72) patients. At the time of assessment, 36%(n=32) patients were febrile. Diffuse respiratory crepitations were present in 58.4%(n=52) patients and 52.8%(n=47) patients had bilateral infiltrates on chest radiograph.

**Table 3: Profile of signs in scrub typhus patients recruited in this study**

	NUMBERS	CENTAGE	PER-
PALLOR	17	19.1	
ICTERUS	16	18	
LYMPHADENOPATHY	1	1.1	
VISIBLE RASH	2	2.2	
OEDEMA	9	10.1	
ESCHAR	67	75.3	
TACHYCARDIA [HR >100/MIN]	72	80.9	
TACHYPNOEA [RR > 24/MIN]	72	80.9	
HYPOTENSION [BP <90/60]	19	21.3	
FEVER [>100 F]	32	36	
HEPATOMEGALY	16	18	
SPLENOMEGALY	14	15.7	
CREPITATIONS	52	58.4	
NECKSTIFFNESS	4	4.5	
CHESTINFILTRATES	47	52.8	

**Table 4: Profile of laboratory parameters of patients recruited in the study**

	MINIMUM	MAXIMUM	MEAN	STANDARD ERROR
Hb [g%]	7.9	16.5	11.8	0.201
WBC count [cell/mm <sup>3</sup> ]	4300	22,700	11,149	426.87
% Neutrophils	36	96	73.12	1.34
Platelets	4000	290000	81898	6608
S.Creatinine [mg/dl]	0.57	4.98	1.48	0.08
S.Sodium [mmol/L]	115	157	131	0.70
S.Potassium [mmol/L]	2.4	5.6	3.8	0.05
S.Bicarbonate [mmol/L]	8.3	30	19.14	0.44
CPK [mg%]	24	5313	831.8	519.18
Total bilirubin [mg%]	0.2	11.4	2.20	0.25
Direct Bilirubin [mg%]	0.1	9.8	1.66	0.21
Protein [g/dl]	4.7	8.3	6.3	0.08
Albumin [g/dl]	1.4	4.3	2.76	0.06
SGOT [mg%]	34	604	149	11.3
SGPT [mg%]	10	574	87.5	7.6
Alkaline phosphatase [mg%]	37	617	185	11.7

The laboratory parameters of the patients with scrub typhus showed that most patients had leucocytosis with a neutrophil predominance.

Thrombocytopenia was a common finding with a mean platelet count of 81,898/mm<sup>3</sup>.

The mean Hemoglobin was 11.8gm%. No major electrolyte abnormalities were noted in the patients.

CPK levels were at borderline levels with mean of 831.8 mg%.

Renal dysfunction was present in a significant proportion of patients with a mean serum creatinine of 1.48 mg/dl.

Hepatic dysfunction in the form of transaminitis was a common finding.

## COMPLICATIONS OF SCRUB TYPHUS

● 1 ORGAN    ● 2 ORGANS    ● 3 ORGANS    ● 4 ORGANS    ● NO ORGANS  
● 5 ORGANS    ● 6 ORGANS

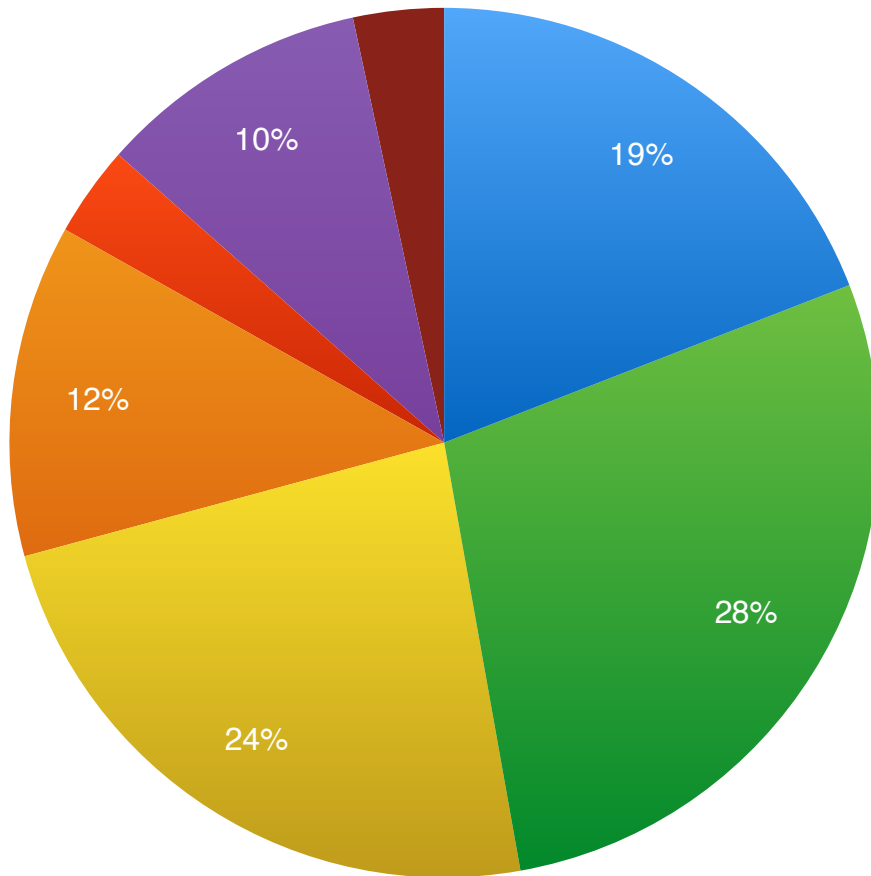


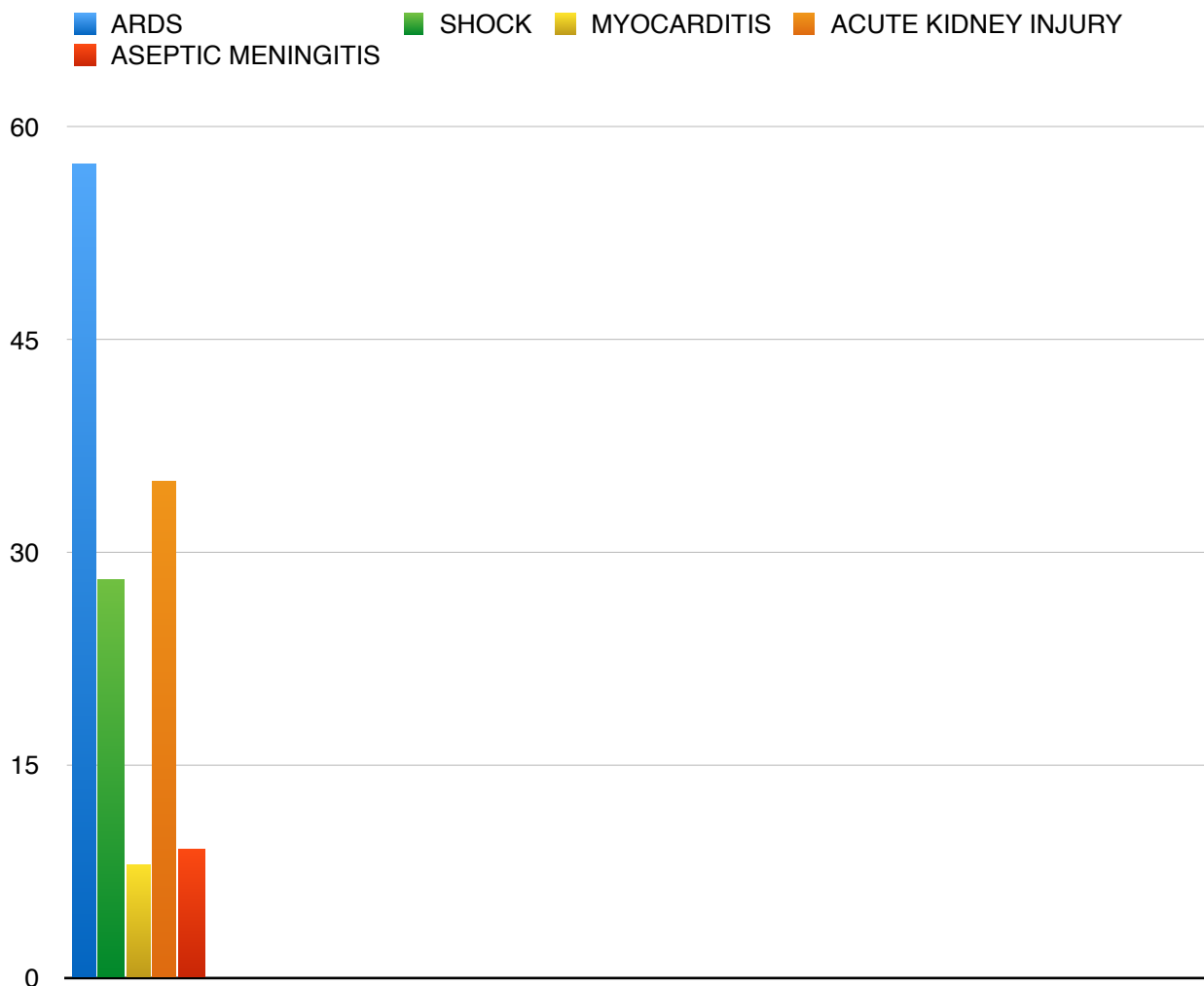
Figure 7: Organ system involvement in scrub typhus

**Table 5: Complications of scrub typhus, numbers and percentages of patients.**

	<b>NUMBERS</b>	<b>PERCENTAGE</b>
<b>ACUTE RESPIRATORY DISTRESS SYNDROME</b>	51	57.3
<b>SHOCK</b>	25	28.1
<b>MYOCARDITIS</b>	7	7.9
<b>ACUTE KIDNEY INJURY</b>	32	36
<b>ASEPTIC MENINGITIS</b>	8	9



The most common complication of scrub typhus observed in this study was acute respiratory distress syndrome (ARDS). It was present in 51(57.3%) patients. Shock and acute kidney injury were present in 28.15(n=25) and 36%(n=32) patients respectively. Other complications such as aseptic meningitis and myocarditis was less commonly observed. Majority of patients had one to three organ systems that were dysfunctional.



**Figure 8: Complications in scrub typhus patients.**

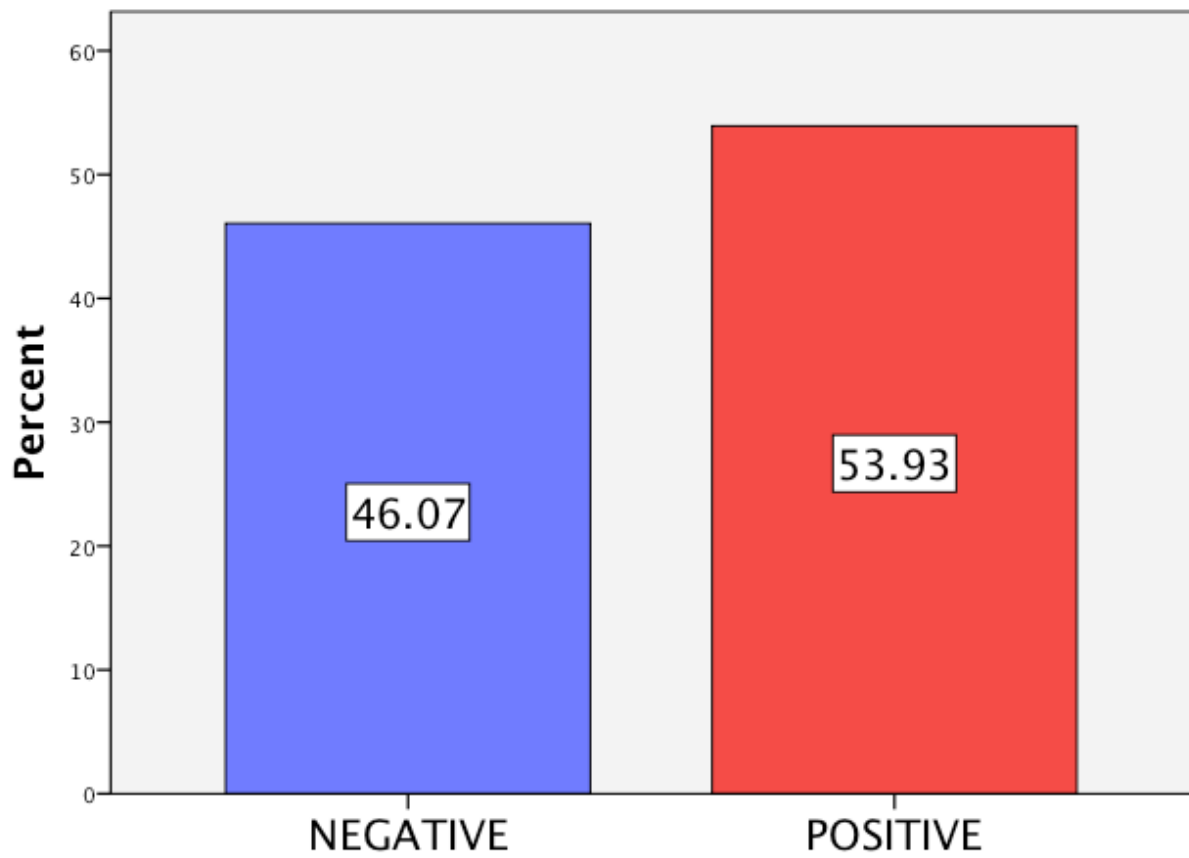
**PRIMARY OUTCOME:**

**I: ESTIMATION OF PREVALENCE AND PATTERNS OF ANTINUCLEAR ANTIBODIES  
IN SCRUB TYPHUS, IN COMPARISON WITH CONTROL GROUPS**

**ANTINUCLEAR ANTIBODIES IN PATIENTS WITH SCRUB TYPHUS**

Of the 89 patients with scrub typhus recruited for the study, serology revealed presence of anti-nuclear antibodies in 78.65%(n=70) patients. Excluding patients who showed weak positive expression of anti-nuclear antibodies, 53.93(n=48)% had anti-nuclear antibodies.

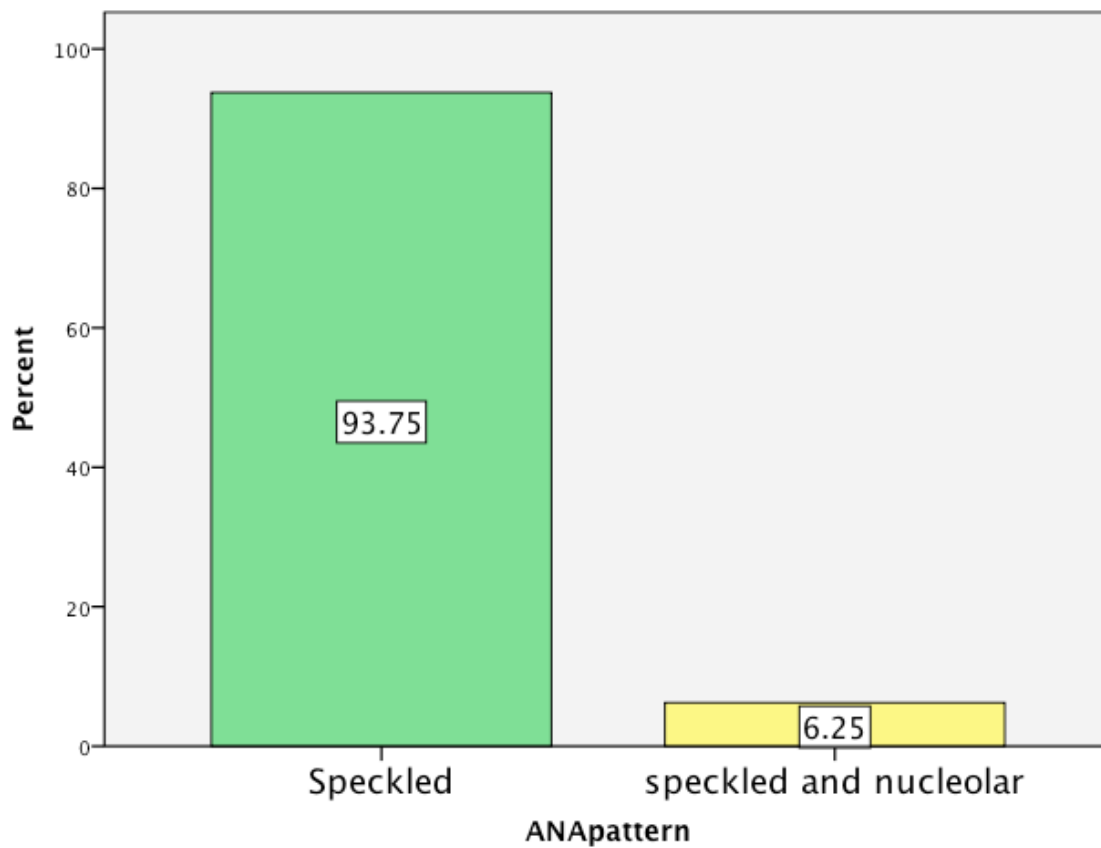
For all further analysis, cases of weak ANA positivity were included with the cases that were negative for ANA expression.



**Figure 9: Prevalence of anti-nuclear antibodies in patients with Scrub typhus**

### PATTERNS OF ANTI-NUCLEAR ANTIBODY EXPRESSION

Of the 48 patients with positive anti-nuclear antibodies, 93.75%(n=45) had a speckled pattern and 6.25%(n=3) had a speckled and nucleolar pattern of anti-nuclear antibodies.



**Figure 10: Patterns of antinuclear antibody expression in scrub typhus**

**COMPARISON OF SCRUB TYPHUS CASES WITH CONTROLS WITH OTHER ACUTE  
FEBRILE ILLNESSES**

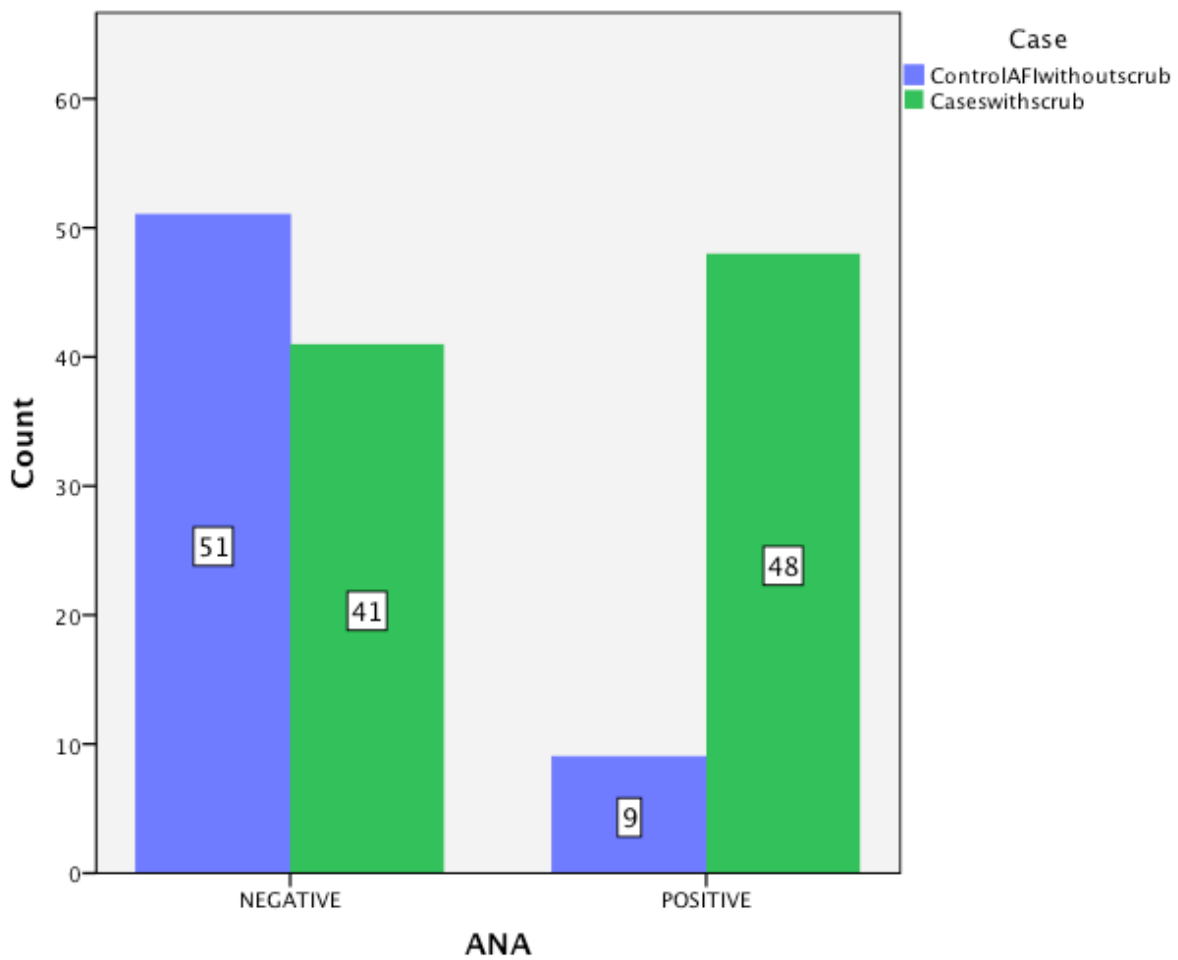
In this study, controls were not adequately matched with scrub typhus patients for age and sex. The p value for age group was 0.046 and for gender was 0.008. Hence, age group and gender was adjusted in further analysis.

**Table 6: Comparison of characteristics of scrub typhus patients with controls with acute febrile illnesses**

	CASE	CONTROL
<b>AGE</b>		
16-29	15	16
30-49	37	13
50-69	24	24
>=70	13	7
<b>GENDER</b>		
MALE	38	39
FEMALE	51	21
<b>ANA</b>		
POSITIVE	41	9
NEGATIVE	48	51
<b>ANA TITRE</b>		
Negative	16	50
1+	23	3
2+	22	6
3+	3	0
Weak+	22	0
Negative with cytoplasmic fluorescence	3	1

## PREVALENCE OF ANTINUCLEAR ANTIBODIES IN CASES IN COMPARISON WITH CONTROLS

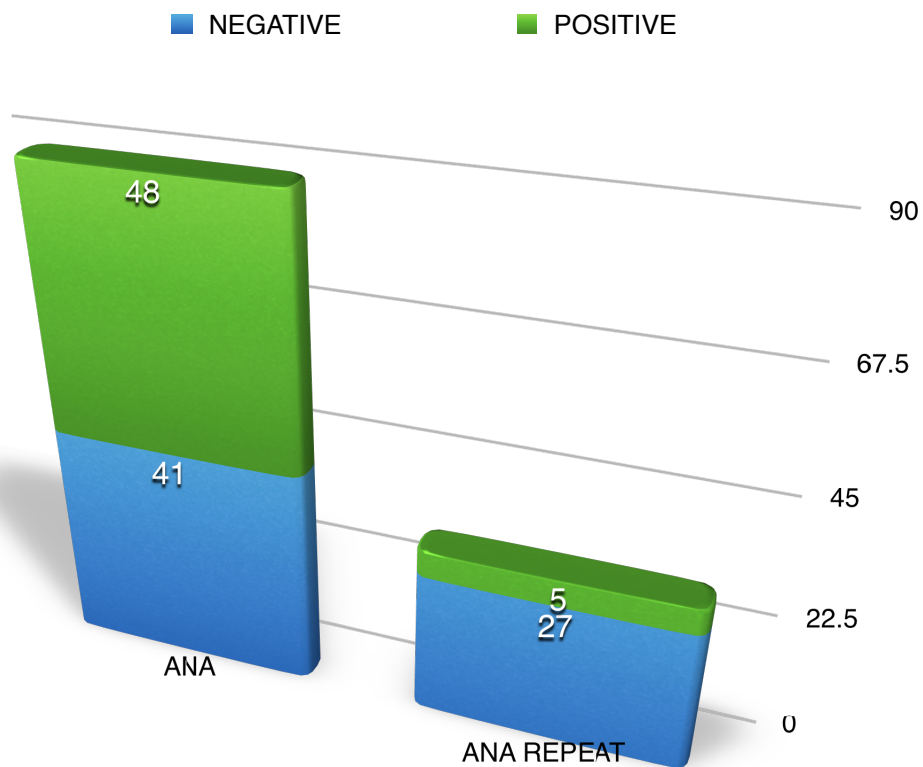
While the prevalence of antinuclear antibodies was 53.93% in patients with scrub typhus, patients with other acute febrile illnesses had an antinuclear antibody prevalence of 15%. This difference was found to be statistically significant with a p value of <0.001.



**Figure 11: Prevalence of antinuclear antibodies in scrub typhus in comparison with other acute febrile illnesses.**

**COMPARISON OF ANTINUCLEAR ANTIBODY PREVALENCE DURING AND 6 WEEKS  
AFTER ILLNESS- IN SCRUB TYPHUS**

While the prevalence of antinuclear antibodies was 53.93% in patients with scrub typhus, on repeating the test for 32 people after a period of 6 weeks, only 5 persisted to be ANA positive(15.62%). This data shows that there is a trend towards returning to baseline ANA positivity in the general population.



**Figure 12: Prevalence of antinuclear antibodies during and 6 weeks after illness (ANA repeat) in patients with scrub typhus**

## **II CORRELATION OF ANTINUCLEAR ANTIBODY EXPRESSION WITH ORGAN DYS- FUNCTION IN SCRUB TYPHUS**

### **CORRELATION OF ANTINUCLEAR ANTIBODY POSITIVITY AND SOFA, APACHE III AND MODS**

On bivariate analysis of antinuclear antibody positivity with organ dysfunction as assessed by the Sequential Organ Failure Assessment scoring that was done on day 1, 3 and 5 of admission, no correlation was found. The multiple organ dysfunction score also showed no correlation with antinuclear antibody positivity. However, bivariate analysis of the Acute physiology and chronic health evaluation (APACHE) III showed a correlation with antinuclear antibody positivity and this was found to be tending towards statistical significance ( $p= 0.07$ ). Antinuclear antibody positivity predicted higher APACHE III scores.



**Table 8: Bivariate analysis of ANA positivity with SOFA Day 1, 3 and 5, MODS and**

**APACHE III scores**

	<b>ODDS RATIO</b>	<b>95% CONFIDENCE INTERVAL</b>	<b>P VALUE</b>
SOFA Day 1	1.06	0.94- 1.19	0.32
SOFA Day 3	1.06	0.94- 1.20	0.32
SOFA Day 5	1.00	0.85- 1.18	0.938
Mutiple Organ dysfunction score	1.25	0.92- 1.69	0.14
<b>APACHE III SCORE</b>	<b>1.01</b>	<b>0.99- 1.03</b>	<b>0.07</b>

**CORRELATION OF ANTINUCLEAR ANTIBODY POSITIVITY WITH ORGAN DYS-  
FUNCTION AND COMPLICATIONS OF SCRUB TYPHUS**

**Table 9: Bivariate analysis of complications of scrub typhus and ANA positivity**

	<b>ODDS RATIO</b>	<b>95% CONFIDENCE INTERVAL</b>	<b>p VALUE</b>
MYOCARDITIS	2.20	0.40- 12.05	0.36
RENAL FAILURE	1.01	0.42- 2.45	0.96
SHOCK	1.08	0.42- 2.75	0.42
<b>ARDS</b>	<b>2.44</b>	<b>1.02- 5.80</b>	<b>0.04</b>
<b>ASEPTIC MENINGITIS</b>	<b>6.65</b>	<b>0.72- 56.63</b>	<b>0.08</b>

**Table 10: Bivariate analysis of individual parameters of SOFA D1 and ANA positivity**

	<b>ODDS RATIO</b>	<b>95% CONFIDENCE INTERVAL</b>	<b>p VALUE</b>
CARDIAC [SOFA]	0.78	0.29- 2.14	0.64
CNS [SOFA]	3.79	0.75- 19.04	0.10
HEMATOLOGY [SOFA]	0.83	0.24- 2.87	0.77
RENAL [SOFA]	1.01	0.43- 2.35	0.43
<b>LIVER [SOFA]</b>	<b>2.25</b>	<b>0.94- 5.39</b>	<b>0.06</b>

Bivariate analysis of organ dysfunction in scrub typhus with antinuclear antibody positivity revealed a positive correlation with acute respiratory distress syndrome [OR- 2.44, 95% CI- 1.02- 5.8, p= 0.04]. There was a correlation with development of aseptic meningitis, which showed a trend towards statistical significance [OR- 6.65, 95% CI- 0.72- 56.63, p= 0.08]. On bivariate analysis of individual parameters of sequential organ failure assessment(SOFA) score, day 1, a positive correlation was found with hepatic dysfunction and antinuclear antibody presence [OR- 2.25, 95% CI- 0.94- 5.39, p- 0.06].

## SECONDARY OUTCOMES

### I. ANTINUCLEAR ANTIBODIES AND DURATION OF HOSPITAL STAY IN SCRUB TYPHUS

On bivariate analysis, there was no correlation between antinuclear antibodies and duration of hospital stay.

### II. ANTINUCLEAR ANTIBODIES AND DURATION OF ICU STAY IN SCRUB TYPHUS

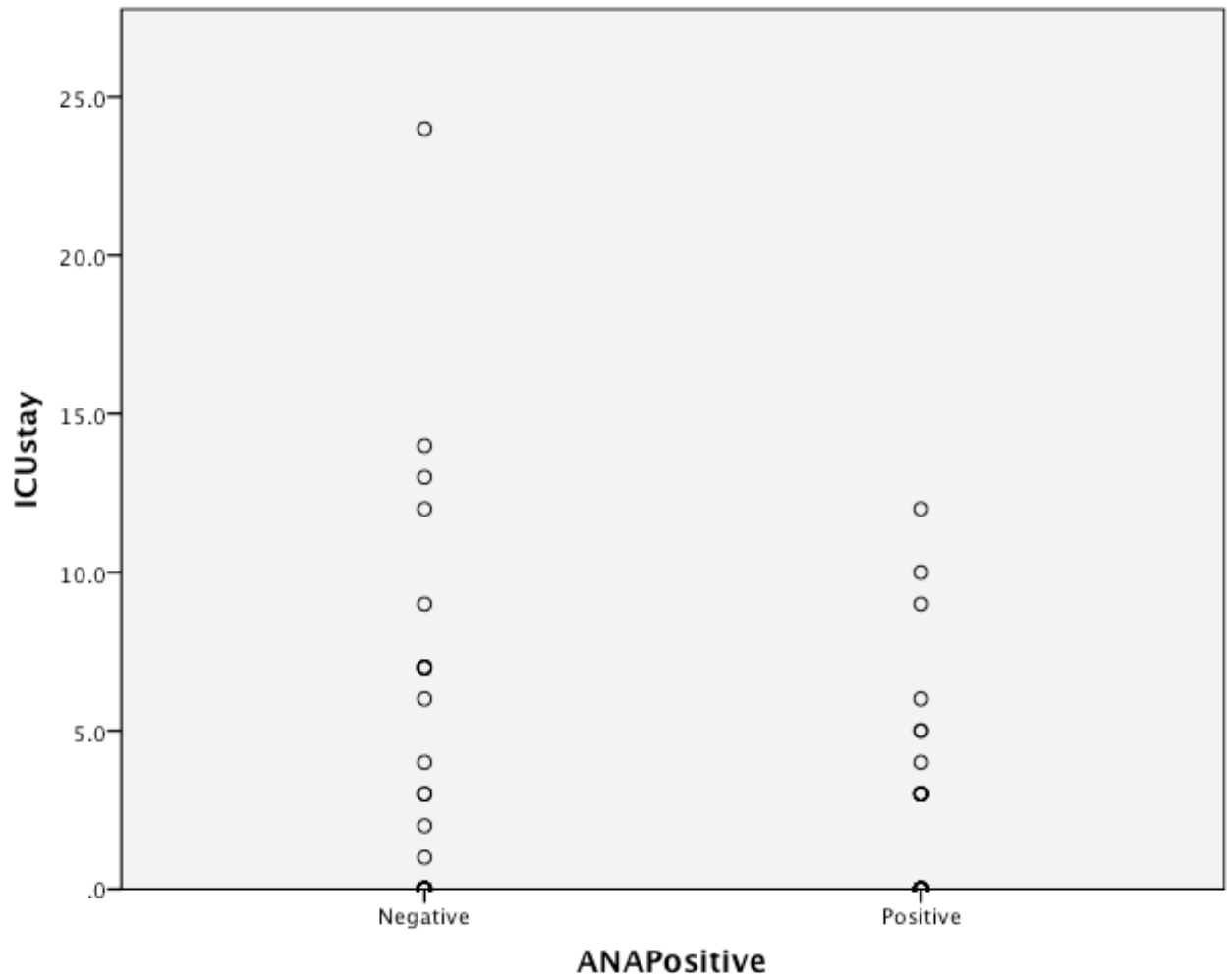
On bivariate analysis, there was no correlation between antinuclear antibodies and duration of ICU stay.

### III. ANTINUCLEAR ANTIBODY POSITIVITY AND MORTALITY IN SCRUB TYPHUS

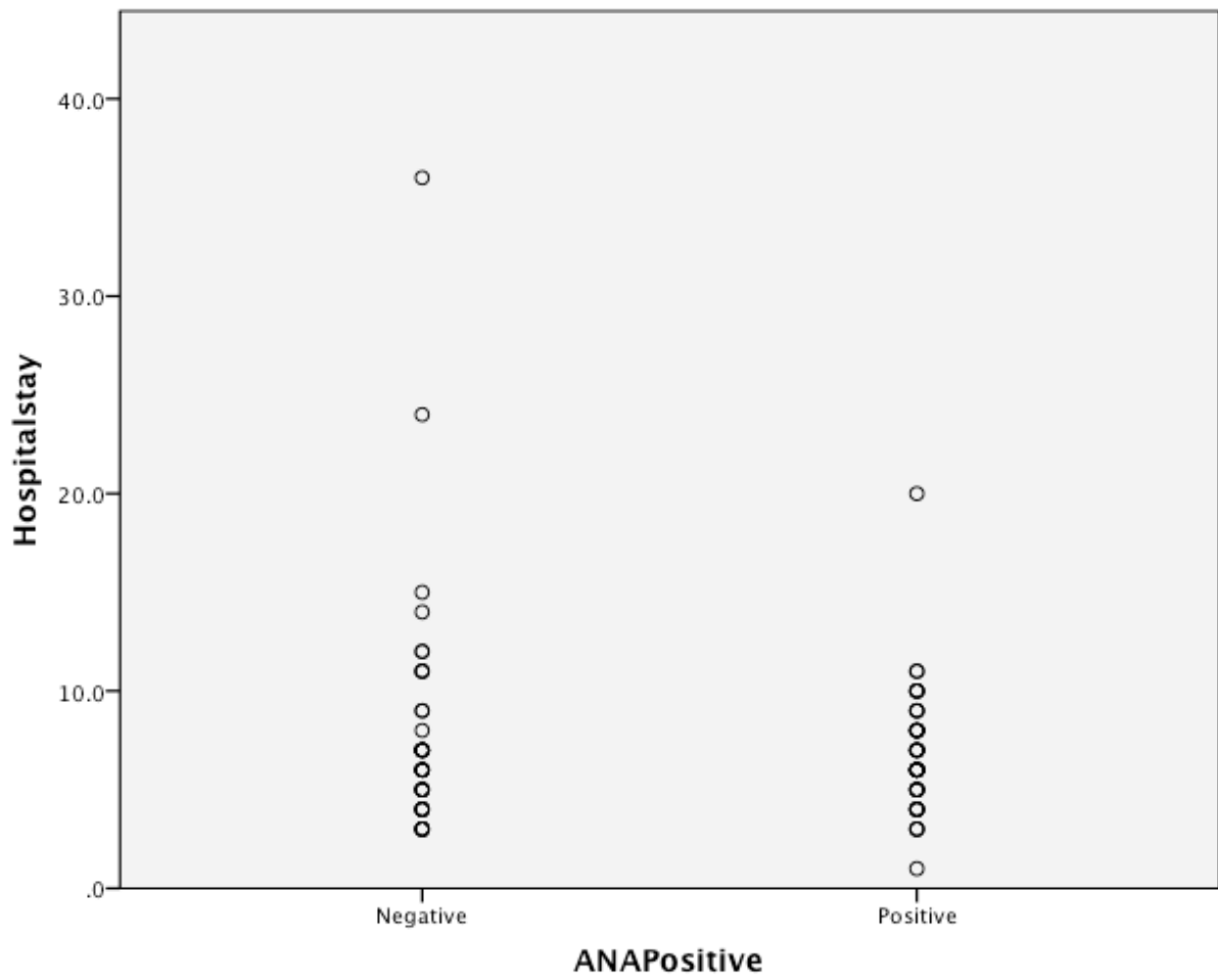
On bivariate analysis, there was no correlation between antinuclear antibody and mortality in scrub typhus.

**Table 11: Bivariate analysis of antinuclear antibody positivity and duration of hospital stay, duration of ICU stay and mortality in scrub typhus**

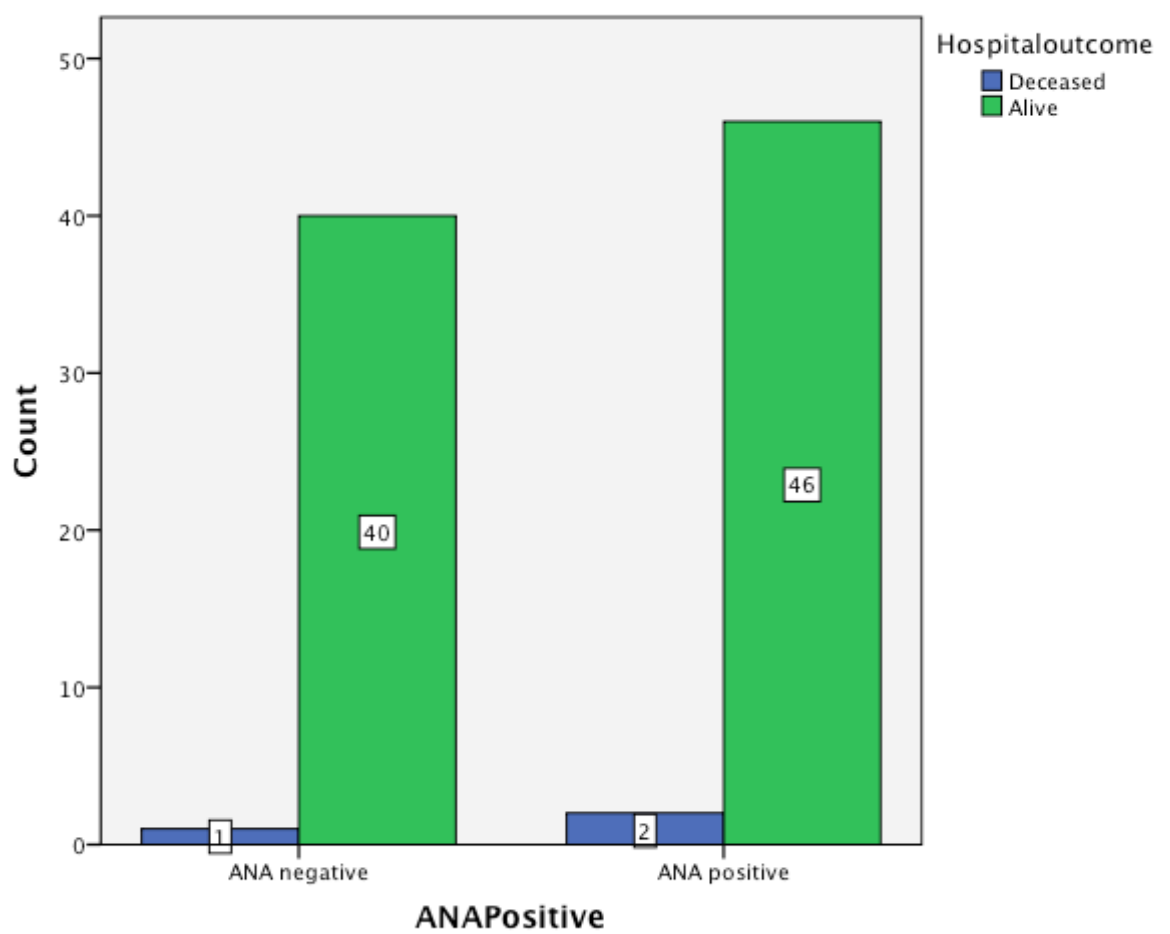
	ODDS RATIO	95% CONFIDENCE INTERVAL	P VALUE
<b>ICU STAY</b>	0.87	0.71- 1.06	0.17
<b>HOSPITAL STAY</b>	0.94	0.85- 1.04	0.29
<b>HOSPITAL OUTCOME</b>	0.58	0.05- 0.67	0.67



**Figure 13: Scatter plot of Antinuclear antibodies in patients with scrub typhus and ICU stay (in days)**



**Figure 14: Scatter plot of Antinuclear antibodies in patients with scrub typhus and Hospital stay(in days)**



**Figure 15: Antinuclear antibodies in patients with scrub typhus and mortality (n=numbers in the bar chart)**

## **DISCUSSION**

To the best of our knowledge, this is the first study that has prospectively evaluated prevalence of anti-nuclear antibody expression and outcomes in patients with scrub typhus.

### **Prevalence and patterns of antinuclear antibodies in patients with scrub typhus:**

The prevalence of antinuclear antibodies in patients with scrub typhus was 53.93%. In the control arm, antinuclear antibodies were present in 15%. This difference was found to be statistically significant ( p value <0.01 ). The prevalence of antinuclear antibodies in the general population is estimated at 3 to 15%. This study has highlighted that patients with scrub typhus have a significantly higher expression of antinuclear antibodies. On including cases which showed weak positivity for antinuclear antibodies, the prevalence was as high as 78.65%. Repeat antinuclear antibody tests were performed in 32 patients after a period of 6 weeks- 5(15.6%) patients persisted to have antinuclear antibodies. This suggests a return to the baseline antinuclear antibody positivity rate of the general population.

The presence of autoantibodies in scrub typhus could suggest molecular mimicry and a non specific activation of the immune system. Since the pathogenesis of scrub typhus involves an infectious systemic vasculitis, presence of these autoantibodies could be a result of the same. Inflammation and stimulation of polyclonal antibody formation probably induces autoantibody formation against self antigens. Antinuclear antibodies have been previously detected in patients with malaria, tuberculosis and other infections. The decrease in titres after 6 weeks suggests that antinuclear antibodies in scrub typhus may not be a manifestation of true autoimmunity or portend risk of developing lupus. Decrease in titres and absence of antibodies after the convalescence period may also suggest that these autoantibodies may be acute phase reactants.



The principle site of involvement in scrub typhus is the endothelial cell which results in a vasculopathy and increased microvascular permeability. This has been postulated as the reason for the protean manifestations of this disease ranging from skin to central nervous system involvement. Inflammation is mediated via cytokines and a Th1 response with formation of IFN- $\gamma$  is essential for containment of infection. Recent studies have demonstrated that TNF- $\alpha$  levels can predict severity of illness.

Humoral immunity in scrub typhus is not well studied and at present, its role in infection is not clear. Further studies are essential to further understand the mechanism and pathogenesis behind autoantibody formation in scrub typhus.

In this study, the most commonly expressed pattern of antinuclear antibodies was the speckled pattern(93.75%). The speckled pattern of antinuclear antibodies is seen in autoimmune diseases such as lupus, mixed connective tissue disease, polymyositis and Sjogren's syndrome. This pattern has also been recently observed in patients with malaria. A recent study has used presence of speckled pattern of antinuclear antibodies as a surrogate marker for detection of chronic malaria.

The rest of the patients who had positive antinuclear antibodies expressed a speckled and nucleolar pattern(6.25%). 3(3.37%) patients had a cytoplasmic fluorescence pattern. The reason behind the expression of the speckled pattern of antinuclear antibodies needs to be studied further for better understanding.

### **Antinuclear antibodies and outcomes in scrub typhus**

On bivariate analysis, we did not find a correlation between antinuclear antibody positivity and sequential organ failure assessment scores on day 1, 3 and 5 of admission. There was no correlation with multi organ dysfunction scores. However, bivariate analysis of the APACHE III scores and antinuclear antibody positivity showed correlation which was tending towards statistical significance. [OR- 1.01, 95%CI- 0.99- 1.03, p- 0.07].

On analysis of the individual organ systems involved, it was noted that antinuclear antibodies correlated with the development of ARDS [ OR- 2.44, 95% CI- 1.02- 5.80, p- 0.04]. The development of neurological complications such as aseptic meningitis also appeared to correlate with a trend towards clinical significance [OR- 6.65, 95% CI- 0.72- 56.63, p-0.08]. It is also interesting to note that all patients who developed seizures with scrub typhus were positive for antinuclear antibodies. On assessment of the individual parameters of the SOFA scores on day 1, it was found that a correlation existed between antinuclear antibody positivity and hepatic dysfunction, which also showed a trend towards significance [OR- 2.25, 95% CI- 0.94- 5.39, p- 0.06]

Hence, on analysis of outcomes, antinuclear antibodies showed a positive correlation with APACHE III scores and the development of neurological, hepatic and respiratory complications of scrub typhus.

### **Antinuclear antibodies and duration of hospital and ICU stay**

On analysis, no correlation was found between the presence of antinuclear antibodies in scrub typhus and the duration of hospitalisation. Antinuclear antibody positivity had no effect on the duration of ICU stay in these patients with scrub typhus.

### **Mortality in scrub typhus and antinuclear antibodies**

There were 3 deaths due to scrub typhus in this study. The mortality was 3.37%. On bivariate analysis, no correlation was found between mortality due to scrub typhus and the presence of antinuclear antibodies.

## **LIMITATIONS**

- A small sample size has been an important limitation in our study. The sample size under each subgroup was too small to perform tests of significance in a meaningful manner.
- The second limitation was that the controls were not adequately matched for age, sex and other confounding variables. We have taken some steps to adjust for this in the analysis.
- Controls were included in the study to adjust for the presence of anti-nuclear antibody presence in other infections.
- Another important limitation was the non-availability of repeat ANA samples in a significant number of patients who initially tested positive for anti-nuclear antibodies.
- In our analysis, we have attempted to adjust for all potential confounders. However, the possibility of other unmeasured confounders cannot entirely be excluded.
- In this study, antinuclear antibodies were found in a significant number of cases in comparison with controls. However, antinuclear antibody had no correlation with outcomes or severity of illness in our analysis. It may be that the sample size studied was not adequately powered to detect a significant difference in outcomes. This study highlights the need for further studies in this area to understand the mechanism of autoantibody production in scrub typhus and the significance of the same.

## **CONCLUSIONS**

- In patients with Scrub typhus, antinuclear antibodies are found in a significant proportion of patients.
- This is significantly different from the antinuclear antibody positivity seen in other acute febrile illness.
- It appears to be an acute phenomenon, as there is a tendency for antinuclear antibodies to become negative after the acute phase of illness.
- Antinuclear antibody positivity was not found to correlate with the sequential organ failure assessment(SOFA) scores, duration of hospital stay or mortality.
- However, a correlation was found between antinuclear antibody positivity and APACHE III scores, suggesting that presence of these antibodies may predict a worse outcome.

- We also noted a significant correlation between the presence of antinuclear antibodies and the development of neurological, respiratory and hepatic complications in scrub typhus, further suggesting a vasculitic mechanism behind these complications.
- This may be an epiphenomenon or there may be a true causal relationship.
- Further studies of larger numbers are required to understand the mechanisms and implications of antinuclear antibody production in scrub typhus.

## **REFERENCES**

1. Tamura A, Ohashi N, Urakami H, Miyamura S. Classification of *Rickettsia tsutsugamushi* in a New Genus, *Orientia* gen. nov., as *Orientia tsutsugamushi* comb. nov. *Int J Syst Bacteriol.* 1995 Jul 1;45(3):589–91.
2. Kelly DJ, Fuerst PA, Ching W-M, Richards AL. Scrub typhus: the geographic distribution of phenotypic and genotypic variants of *Orientia tsutsugamushi*. *Clin Infect Dis Off Publ Infect Dis Soc Am.* 2009 Mar 15;48 Suppl 3:S203–230.
3. Rajapakse S, Rodrigo C, Fernando D. Scrub typhus: pathophysiology, clinical manifestations and prognosis. *Asian Pac J Trop Med.* 2012 Apr;5(4):261–4.
4. Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JAJ, Thomas EM, et al. Acute undifferentiated febrile illness in adult hospitalized patients: the disease spectrum and diagnostic predictors - an experience from a tertiary care hospital in South India. *Trop Doct.* 2010 Oct;40(4):230–4.
5. Chrispal A, Boorugu H, Gopinath KG, Prakash JAJ, Chandy S, Abraham OC, et al. Scrub typhus: an unrecognized threat in South India - clinical profile and predictors of mortality. *Trop Doct.* 2010 Jul;40(3):129–33.
6. Varghese GM, Trowbridge P, Janardhanan J, Thomas K, Peter JV, Mathews P, et al. Clinical profile and improving mortality trend of scrub typhus in South India. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis.* 2014 Jun;23:39–43.
7. Hackstadt T. The biology of rickettsiae. *Infect Agents Dis.* 1996 Jun;5(3):127–43.

8. Farrar J, Hotez P, Junghanss T, Kang G, Lalloo D, White NJ. *Manson's Tropical Diseases: Expert Consult - Online*. Elsevier Health Sciences; 2013. 1664 p.
9. Raoult D, Roux V. Rickettsioses as paradigms of new or emerging infectious diseases. *Clin Microbiol Rev*. 1997 Oct;10(4):694–719.
10. Azad AF, Beard CB. Rickettsial pathogens and their arthropod vectors. *Emerg Infect Dis*. 1998;4(2):179–86.
11. Wells GM, Woodward TE, Fiset P, Hornick RB. Rocky mountain spotted fever caused by blood transfusion. *JAMA J Am Med Assoc*. 1978 Jun 30;239(26):2763–5.
12. Lee N, Ip M, Wong B, Lui G, Tsang OTY, Lai JY, et al. Risk Factors Associated with Life-threatening Rickettsial Infections. *Am J Trop Med Hyg*. 2008 Jun 1;78(6):973–8.
13. Watt G, Parola P. Scrub typhus and tropical rickettsioses. *Curr Opin Infect Dis*. 2003 Oct;16(5):429–36.
14. Mahajan SK. Scrub typhus. *J Assoc Physicians India*. 2005 Nov;53:954–8.
15. Mathai E, Rolain JM, Verghese GM, Abraham OC, Mathai D, Mathai M, et al. Outbreak of Scrub Typhus in Southern India during the Cooler Months. *Ann N Y Acad Sci*. 2003 Jun 1;990(1):359–64.
16. Kim S, Kim JS, Lee H. Epidemiological characteristics of scrub typhus in Korea, 2009. *Osong Public Health Res Perspect*. 2010 Dec;1(1):55–60.
17. Kim D-M, Kim KY, Nam HS, Kweon SS, Park M-Y, Ryu SY. Risk-factors for human infection with *Orientia tsutsugamushi*: a case-control study in Korea. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis*. 2008 Feb;14(2):174–7.



18. Kuo C-C, Huang J-L, Ko C-Y, Lee P-F, Wang H-C. Spatial analysis of scrub typhus infection and its association with environmental and socioeconomic factors in Taiwan. *Acta Trop*. 2011 Nov;120(1-2):52–8.
19. Li T, Yang Z, Dong Z, Wang M. Meteorological factors and risk of scrub typhus in Guangzhou, southern China, 2006-2012. *BMC Infect Dis*. 2014;14:139.
20. Lyu Y, Tian L, Zhang L, Dou X, Wang X, Li W, et al. A case-control study of risk factors associated with scrub typhus infection in Beijing, China. *PloS One*. 2013;8(5):e63668.
21. Sharma PK, Ramakrishnan R, Hutin YJF, Barui AK, Manickam P, Kakkar M, et al. Scrub typhus in Darjeeling, India: opportunities for simple, practical prevention measures. *Trans R Soc Trop Med Hyg*. 2009 Nov;103(11):1153–8.
22. Kweon S-S, Choi J-S, Lim H-S, Kim J-R, Kim K-Y, Ryu S-Y, et al. A community-based case-control study of behavioral factors associated with scrub typhus during the autumn epidemic season in South Korea. *Am J Trop Med Hyg*. 2009 Mar;80(3):442–6.
23. Lee C-S, Hwang J-H, Lee H-B, Kwon K-S. Risk Factors Leading to Fatal Outcome in Scrub Typhus Patients. *Am J Trop Med Hyg*. 2009 Sep 1;81(3):484–8.
24. Walker DH. Rickettsiae and rickettsial infections: the current state of knowledge. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007 Jul 15;45 Suppl 1:S39–44.
25. Paris DH, Shelite TR, Day NP, Walker DH. Unresolved Problems Related to Scrub Typhus: A Seriously Neglected Life-Threatening Disease. *Am J Trop Med Hyg*. 2013 Aug 7;89(2):301–7.

26. Lee J-H, Cho N-H, Kim S-Y, Bang S-Y, Chu H, Choi M-S, et al. Fibronectin facilitates the invasion of *Orientia tsutsugamushi* into host cells through interaction with a 56-kDa type-specific antigen. *J Infect Dis*. 2008 Jul 15;198(2):250–7.
27. Mansueto P, Vitale G, Cascio A, Seidita A, Pepe I, Carroccio A, et al. New Insight into Immunity and Immunopathology of Rickettsial Diseases. *J Immunol Res*. 2011 Sep 6;2012:e967852.
28. Moron CG, Popov VL, Feng HM, Wear D, Walker DH. Identification of the target cells of *Orientia tsutsugamushi* in human cases of scrub typhus. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2001 Aug;14(8):752–9.
29. Kundin WD, Liu C, Harmon P, Rodina P. Pathogenesis of Scrub Typhus Infection (*Rickettsia Tsutsugamushi*) as Studied by Immunofluorescence. *J Immunol*. 1964 Nov 1;93(5):772–81.
30. Allen AC, Spitz S. A Comparative Study of the Pathology of Scrub Typhus (*Tsutsugamushi* Disease) and Other Rickettsial Diseases. *Am J Pathol*. 1945 Jul;21(4):603–81.
31. Iwasaki H, Mizoguchi J, Takada N, Tai K, Ikegaya S, Ueda T. Correlation between the concentrations of tumor necrosis factor-alpha and the severity of disease in patients infected with *Orientia tsutsugamushi*. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2010 Apr;14(4):e328–333.
32. Ogawa M, Hagiwara T, Kishimoto T, Shiga S, Yoshida Y, Furuya Y, et al. Scrub typhus in Japan: epidemiology and clinical features of cases reported in 1998. *Am J Trop Med Hyg*. 2002 Aug;67(2):162–5.
33. Varghese GM, Janardhanan J, Trowbridge P, Peter JV, Prakash JAJ, Sathyendra S, et al. Scrub typhus in South India: clinical and laboratory manifestations, genetic variability, and outcome. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2013 Nov;17(11):e981–987.

34. Kim D-M, Won KJ, Park CY, Yu KD, Kim HS, Yang TY, et al. Distribution of Eschars on the Body of Scrub Typhus Patients: A Prospective Study. *Am J Trop Med Hyg.* 2007 May 1;76(5):806–9.
35. Kundavaram AP, Jonathan AJ, Nathaniel SD, Varghese GM. Eschar in scrub typhus: a valuable clue to the diagnosis. *J Postgrad Med.* 2013 Sep;59(3):177–8.
36. Charoensak A, Chawalparit O, Suttinont C, Niwattayakul K, Losuwanaluk K, Silpasakorn S, et al. Scrub typhus: chest radiographic and clinical findings in 130 Thai patients. *J Med Assoc Thail Chotmaihet Thangphaet.* 2006 May;89(5):600–7.
37. Chen H-C, Chang H-C, Chang Y-C, Liu S-F, Su M-C, Huang K-T, et al. Chest radiographic presentation in patients with scrub typhus. *Trans R Soc Trop Med Hyg.* 2012 Jan 1;106(1):48–53.
38. Wang C-C, Liu S-F, Liu J-W, Chung Y-H, Su M-C, Lin M-C. Acute Respiratory Distress Syndrome in Scrub Typhus. *Am J Trop Med Hyg.* 2007 Jun 1;76(6):1148–52.
39. Park JS, Jee YK, Lee KY, Kim KY, Myong NH, Seo PW. Acute respiratory distress syndrome associated with scrub typhus: diffuse alveolar damage without pulmonary vasculitis. *J Korean Med Sci.* 2000 Jun;15(3):343–5.
40. Aronoff DM, Watt G. Prevalence of relative bradycardia in *Orientia tsutsugamushi* infection. *Am J Trop Med Hyg.* 2003 Apr;68(4):477–9.
41. Yotsukura M, Aoki N, Fukuzumi N, Ishikawa K. Review of a case of tsutsugamushi disease showing myocarditis and confirmation of *Rickettsia* by endomyocardial biopsy. *Jpn Circ J.* 1991 Feb;55(2):149–53.

42. Bharathi S, Jayachandran S, Senthil N, Sujatha S. Scrub typhus causing myocarditis and ARDS: A case report. *Heart India*. 2013;1(3):85.
43. Hoshino C, Narita M, Yamabe A, Sekikawa Y, Ishihara K, Ikeda H, et al. Scrub Typhus-Induced Serious Gastric Ulcer Bleeding. *Intern Med*. 2011;50(21):2675–7.
44. Kim SJ, Chung IK, Chung IS, Song DH, Park SH, Kim HS, et al. The clinical significance of upper gastrointestinal endoscopy in gastrointestinal vasculitis related to scrub typhus. *Endoscopy*. 2000 Dec;32(12):950–5.
45. Aung-Thu null, Supanaranond W, Phumiratanaprapin W, Phonrat B, Chinprasatsak S, Ratana-jaratroj N. Gastrointestinal manifestations of septic patients with scrub typhus in Maharat Nakhon Ratchasima Hospital. *Southeast Asian J Trop Med Public Health*. 2004 Dec;35(4):845–51.
46. Basu G, Chrispal A, Boorugu H, Gopinath KG, Chandy S, Prakash JAJ, et al. Acute kidney injury in tropical acute febrile illness in a tertiary care centre—RIFLE criteria validation. *Nephrol Dial Transplant*. 2011 Feb 1;26(2):524–31.
47. Kumar V, Kumar V, Yadav AK, Iyengar S, Bhalla A, Sharma N, et al. Scrub typhus is an under-recognized cause of acute febrile illness with acute kidney injury in India. *PLoS Negl Trop Dis*. 2014 Jan;8(1):e2605.
48. Yum KS, Na S-J, Lee KO, Ko JH. Scrub typhus meningo-encephalitis with focal neurologic signs and associated brain MRI abnormal findings: literature review. *Clin Neurol Neurosurg*. 2011 Apr;113(3):250–3.

49. Varghese GM, Mathew A, Kumar S, Abraham OC, Trowbridge P, Mathai E. Differential diagnosis of scrub typhus meningitis from bacterial meningitis using clinical and laboratory features. *Neurol India*. 2013 Feb;61(1):17–20.
50. Boorugu H, Chrispal A, Gopinath KG, Chandy S, Prakash JJ, Abraham AM, et al. Central nervous system involvement in scrub typhus. *Trop Doct*. 2014 Jan;44(1):36–7.
51. Mahajan SK, Rolain JM, Kanga A, Raoult D. Scrub typhus involving central nervous system, India, 2004-2006. *Emerg Infect Dis*. 2010 Oct;16(10):1641–3.
52. Lee M-S, Lee J-H, Lee H-S, Chang H, Kim Y-S, Cho K-H, et al. Scrub typhus as a possible aetiology of Guillain-Barré syndrome: two cases. *Ir J Med Sci*. 2009 Sep;178(3):347–50.
53. Chiou Y-H, Yang C-J, Lai T-H. Scrub typhus associated with transient parkinsonism and myoclonus. *J Clin Neurosci Off J Neurosurg Soc Australas*. 2013 Jan;20(1):182–3.
54. Chen P-H, Hung K-H, Cheng S-J, Hsu K-N. Scrub typhus-associated acute disseminated encephalomyelitis. *Acta Neurol Taiwanica*. 2006 Dec;15(4):251–4.
55. Chogle AR. Diagnosis and treatment of scrub typhus--the Indian scenario. *J Assoc Physicians India*. 2010 Jan;58:11–2.
56. Koh GCKW, Maude RJ, Paris DH, Newton PN, Blacksell SD. Diagnosis of Scrub Typhus. *Am J Trop Med Hyg*. 2010 Mar 1;82(3):368–70.
57. Blacksell SD, Bryant NJ, Paris DH, Doust JA, Sakoda Y, Day NPJ. Scrub typhus serologic testing with the indirect immunofluorescence method as a diagnostic gold standard: a lack of consensus leads to a lot of confusion. *Clin Infect Dis Off Publ Infect Dis Soc Am*. 2007 Feb 1;44(3):391–401.

58. Solomon DH, Kavanaugh AJ, Schur PH, American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. *Arthritis Rheum.* 2002 Aug;47(4):434–44.
59. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, et al. Range of antinuclear antibodies in “healthy” individuals. *Arthritis Rheum.* 1997 Sep;40(9):1601–11.
60. Berlin T, Zandman-Goddard G, Blank M, Matthias T, Pfeiffer S, Weis I, et al. Autoantibodies in nonautoimmune individuals during infections. *Ann N Y Acad Sci.* 2007 Jun;1108:584–93.
61. Sarzi-Puttini P, Atzeni F, Capsoni F, Lubrano E, Doria A. Drug-induced lupus erythematosus. *Autoimmunity.* 2005 Nov;38(7):507–18.
62. Tan EM. Autoantibodies to nuclear antigens (ANA): their immunobiology and medicine. *Adv Immunol.* 1982;33:167–240.
63. Pisetsky DS, Vrabie IA. Antibodies to DNA: infection or genetics? *Lupus.* 2009 Nov 1;18(13):1176–80.
64. Cainelli F, Betterle C, Vento S. Antinuclear antibodies are common in an infectious environment but do not predict systemic lupus erythematosus. *Ann Rheum Dis.* 2004 Dec;63(12):1707–8.
65. Adebajo AO, Charles P, Maini RN, Hazleman BL. Autoantibodies in malaria, tuberculosis and hepatitis B in a west African population. *Clin Exp Immunol.* 1993 Apr;92(1):73–6.
66. Hommel B, Charuel J-L, Jaureguiberry S, Arnaud L, Courtin R, Kassab P, et al. Chronic malaria revealed by a new fluorescence pattern on the antinuclear autoantibodies test. *PloS One.* 2014;9(2):e88548.

## **APPENDIX**

### **List of annexure included:**

**Annexure I- Patient information and consent form**

**Annexure II- Data abstraction form**

**Annexure III-List of figures and tables**

**Annexure IV-Standard operation protocol**

**Annexure V- Data sheet**

## ANNEXURE I- PATIENT INFORMATION AND CONSENT SHEET

### *Anti nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus*

#### Information sheet

You are being requested to participate in a study to see if anti-nuclear body expression is present in Scrub typhus and to see whether it can be used to predict outcomes in Scrub typhus infection. We hope to include about 90 people from this hospital in this study.

#### **What is Scrub typhus?**

Scrub typhus is a febrile illness commonly seen in South India, especially during the cooler months.

It is caused by rickettsiae and is transmitted by the bites of infected, immature mites(chiggers) that normally reside on rats.

It is not transmitted directly from person to person.

Infection leads to an inflammation of blood vessels- 'vasculitis'. This has a wide variety of manifestations such as fever, headache, cough, rash etc.

Patients are found to have this disease on the basis of classical signs like an eschar and blood tests like the IgM ELISA

Occasionally some patients are found to have a more severe form of illness with a poor outcome.

#### **What is ANA and how is it related to Scrub typhus?**

Antibodies are proteins that are made as part of an immune response. Anti nuclear antibody is an antibody or a substance of immunity that the body produces, which fights against the person's own body. Some patients with Scrub typhus also express this anti-



body. We are attempting to study if this antibody leads to a poor outcome in patients with Scrub typhus.

**If you take part what will you have to do?**

If you agree to participate in this study, we will perform some additional blood tests on you, such as the ANA and Scrub IgM ELISA tests. Thereafter, we will follow you during the course of your illness to assess how your body is coping with the illness and also to look out for any serious damage caused by the illness.

**Can you withdraw from this study after it starts?**

Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

**What will happen if you develop any study related injury?**

There will be no injury related to this study as we are only performing an additional blood test on you, with relation to the study.

**Will you have to pay for the ANA blood test?**

The additional blood test being done for the study will be free of cost. All other treatment of Scrub typhus will continue according to the hospital's treatment protocol and the usual arrangements that you have with the hospital will decide how much you pay for this.

**What happens after the study is over?**

We will follow you up during the course of your illness and stay in hospital. The results of this study may be used in future for the treatment of scrub typhus.

**CONSENT TO TAKE PART IN A CLINICAL TRIAL**

Study Title: *Anti nuclear antibody expression and its relationship to severity of illness, organ dysfunction and outcomes in Scrub typhus.*

Study Number:

Participant's name:

Date of Birth / Age (in years):

\_\_\_\_\_

\_\_\_\_\_, son/daughter of \_\_\_\_\_

- Declare that I have read the information sheet provide to me regarding this study and have clarified any doubts that I had
- I also understand that my participation in this study is entirely voluntary and that I am free to withdraw permission to continue to participate at any time without affecting my usual treatment or my legal rights
- I understand that I will receive free treatment for any study related injury or adverse event but I will not receive any other financial compensation
- I understand that the study staff and institutional ethics committee will not need my permission to look at my health records even if I withdraw from the trial. I agree to this access
- I understand that my identity will not be revealed in any information released to third parties or published
- I voluntarily agree to take part in this study

Name:

Signature:

Date:

**ANNEXURE II- DATA ABSTRACTION FORM ANA EXPRESSION IN SCRUB TYPHUS**

**Serial No:**

**Hospital No:**

**Name:**  **Age:**

**Sex:** Male / Female

**Address:**

**Occupation:**

**Contact number:**

**Risk factors/Co-morbidities:**

**Symptomatology at presentation:**

Symptomatology	Duration of symptom	Symptomatology	Duration of symptom
Fever		Myalgia	
Headache		Abdominal pain	
Nausea/Vomiting		Breathlessness	
Rash		Arthralgia	
Cough		Jaundice	
Altered sensorium		Oliguria	
Seizures		Bleeding	

**Signs:**

Pallor		Tachycardia >100		Splenomegaly	
Icterus		SpO2		Petechiae	
Lymphadenopathy		Tachypnea >20		Crepitations	
Rash		Hypotension <90		Altered sensorium	
Oedema		Fever		Neck stiffness	
Eschar		Hepatomegaly		LV S3	

**Investigations:**

Hb		Potassium		Protein	
TLC		Bicarbonate		Albumin	
% Neutrophils		CPK		SGOT	
Platelets		Total bilirubin		SGPT	
Creatinine		Direct bilirubin		ALP	
Sodium		SGOT		Chest infiltrates	

ANA		Pattern and titer		Repeat ANA	
-----	--	-------------------	--	------------	--

**SOFA details:**

Parameter	Day 1	Day 3	Day 5
Respiratory			
Platelets			
Vasoactive			
GCS score			
Bilirubin score			
Renal score			
<b>TOTAL SCORE</b>			

DAY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
RIFLE															
VENTILATION															
VASOACTIVES															

**Other complications:**

ARDS		Myocarditis		Aseptic meningitis	
Shock		Renal failure [RIFLE]		Pulmonary embolism	

**Use of Vasoactive agents:**

Duration:

**Ventilation and duration :**

Ventilated: Yes / No NIV / Invasive Duration of ventilation : NIV\_\_\_ INV\_\_\_

**Duration of ICU stay (days):**

**Duration of hospital stay (days):**

**Hospital outcome:** Dead / Alive / Discharged at request Probable cause(s) of death:

**Bill:**

**TABLE 1a**

APACHE III scoring system, comprised of the sum of three components: an acute physiology score, an age score, and a chronic health problems score. Scores range from 0 to 299 (physiology, 0 to 252; chronic health evaluation, 0 to 23; age, 0 to 24), with higher values representing a worse prognosis.

<b>Pulse</b>		8	5	0	1	5	7	13	17
		≤ 39	40-49	50-99	100-109	110-119	120-139	140-154	≥ 155
<b>Mean BP (mmHg)</b>		23	15	7	6	0	4	7	10
		≤ 39	40-59	60-69	70-79	80-99	100-119	120-129	≥ 140
<b>Temperature (°C)</b>		20	16	13	8	2	0	4	
		≤ 32.9	33-33.4	33.5-33.9	34-34.9	35-35.9	36-36.9	≥ 40	
<b>Respiratory Rate</b>		17	8	7	0	6	9	11	18
		≤ 5	6-11	12-13	14-24	25-34	35-39	40-49	≥ 50
<b>PaO<sub>2</sub>* (mmHg)</b>		15	5	2	0				
		≤ 49	50-69	70-79	≥ 80				
<b>AaDO<sub>2</sub>** (mmHg)</b>		0	7	9	11	14			
		< 100	100-249	250-349	350-499	≥ 500			
<b>Hematocrit (%)</b>		3	0	3					
		≤ 40.9	41-49	≥ 50					
<b>WBC Count (x10<sup>3</sup>/mm<sup>3</sup>)</b>		19	5	0	1	5			
		< 1.0	1.0-2.9	3.0-19.9	20-24.9	≥ 25			
<b>Serum Creatinine† (mg/dl) without ARF</b>		3	0	4	7				
		≤ 0.4	0.5-1.4	1.5-1.94	≥ 1.95				
<b>Serum Creatinine (mg/dl) with ARF</b>		0	10						
		0-1.4	≥ 1.5						
<b>Urine Output (cc/day)</b>		15	8	7	5	4	0	1	
		≤ 399	400-599	600-899	900-1499	1500-1999	2000-3999	≥ 4000	
<b>Serum BUN (mg/dl)</b>		0	2	7	11	12			
		≤ 16.9	17-19	20-39	40-79	≥ 80			
<b>Serum Na<sup>+</sup> (mEq/L)</b>		3	2	0	4				
		≤ 119	120-134	135-154	≥ 155				
<b>Serum Albumin (g/dl)</b>		11	6	0	4				
		≤ 1.9	2.0-2.4	2.5-4.4	≥ 4.5				
<b>Serum Bilirubin (mg/dl)</b>		0	5	6	8	16			
		≤ 1.9	2.0-2.9	3.0-4.9	5.0-7.9	≥ 8.0			
<b>Serum Glucose (mg/dl)</b>		8	9	0	3	5			
		≤ 39	40-59	60-199	200-349	≥ 350			
<b>Age</b>		0	5	11	13	16	17	24	
		≤ 44	45-59	60-64	65-69	70-74	75-84	≥ 85	
<b>Comorbidities</b>		• AIDS 23 • Hepatic Failure 16 • Lymphoma 13 • Metastatic Cancer 11 • Leukemia/Multiple Myeloma 10 • Immune Compromised 10 • Cirrhosis 4							

**APACHE III**

was introduced to address some of the flaws of APACHE II. Although APACHE III resembles APACHE II, it includes new variables such as prior treatment location and the disease requiring ICU admission. In APACHE III scoring, the patient's age and chronic health history are worth up to 47 points. Within 24 hours of ICU admission, 17 physiologic variables are measured and may add up to a maximum of an additional 252 points. The resulting total score, in combination with prior treatment location and principal ICU diagnosis provides a predicted mortality.

**BENEFITS OF APACHE III:**

- Saves lives by better managing the care of critically ill individuals
- Reduces frequency of complications
- Evaluates and improves ICU performance
- Optimizes ICU resource allocation

**TABLE 1b**

APACHE III acute physiology scoring for neurologic abnormalities.

<b>Motor (Verbal) see †</b>		Oriented, Converses	Confused Conversation	Inappropriate Words & Incomprehensible Sounds	No Response
Obeys verbal command	0 / NA	3 / NA	10 / NA	15 / 16	
Localizes pain	3 / NA	8 / NA	13 / NA	15 / 16	
Flexion withdrawal/decorticate rigidity	3 / NA	13 / NA	24 / 24	24 / 33	
Decerebrate rigidity/no response	3 / NA	13 / NA	29 / 29	29 / 48	

**TABLE 1c**

APACHE III acute physiology scoring for acid-base disturbances.

<b>Acute Physiology</b>		pCO <sub>2</sub> < 25	25 to < 30	30 to < 35	35 to < 40	40 to < 45	45 to < 50	50 to < 55	55 to < 60	pCO <sub>2</sub> ≥ 65
pH < 7.15		12							4	
7.15 to < 7.20										
7.20 to < 7.25		9	6	3		2				
7.25 to < 7.30										
7.30 to < 7.35			0		1					
7.35 to < 7.40		5	0		2					
7.40 to < 7.45										
7.45 to < 7.50			0		2					
7.50 to < 7.55		3		12						
7.55 to < 7.60										
7.60 to < 7.65										
pH ≥ 7.65		0								

TABLE 1a SCORE **a**

TABLE 1b SCORE **+** **b**

TABLE 1c SCORE **+** **c**

**APACHE III SCORE = a+b+c**

† Scoring for Eyes open / do not open spontaneously or to painful/verbal stimulation  
 NA = Not applicable

\*\* If FIO<sub>2</sub> = 50%, record AaDO<sub>2</sub>; \*\* Alveolo-arterial Oxygen Difference: If FIO<sub>2</sub> < 50%, record PaO<sub>2</sub>

† Acute renal failure (ARF) is defined as creatinine > 1.5 mg/day and urine output < 400 cc/day and no chronic dialysis.

References: 1. Knaus WA et al. Chest 1991; 100(6): 1616-36. 2. Yung-Chang C et al. Renal Failure 2002; 24(3): 285-96.

## ANNEXURE III- LIST OF TABLES AND FIGURES

### A. FIGURES

**Figure 1:** *Leptotrombidium deliense*, the primary vector of scrub typhus

**Figure 2:** The phylogenetic tree of *Orientia tsutsugamushi*. Cell surface antigen 56kDa is the basis for this classification

**Figure 3:** The ‘tsutsugamushi triangle’, endemic for scrub typhus

**Figure 4:** The organism, *Orientia tsutsugamushi* being phagocytosed by a macrophage

**Figure 5:** Patterns of antinuclear antibodies and the associated diseases

**Figure 6:** Strobe diagram of the progress through phases of the study

**Figure 7:** Organ system involvement in scrub typhus

**Figure 8:** Complications in scrub typhus patients

**Figure 9:** Prevalence of anti-nuclear antibodies in patients with Scrub typhus

**Figure 10:** Patterns of antinuclear antibody expression in scrub typhus

**Figure 11:** Prevalence of antinuclear antibodies in scrub typhus in comparison with other acute febrile illnesses.

**Figure 12:** Prevalence of antinuclear antibodies during and 6 weeks after illness (ANA repeat) in patients with scrub typhus

**Figure 13:** Antinuclear antibodies in patients with scrub typhus and ICU stay

**Figure 14:** Antinuclear antibodies in patients with scrub typhus and Hospital stay

**Figure 15:** Antinuclear antibodies in patients with scrub typhus and mortality

## **B. TABLES**

**Table 1: Baseline characteristics of the study population**

**Table 2: Profile of symptoms in scrub typhus patients recruited in the study (duration in days)**

**Table 3: Profile of signs in scrub typhus patients recruited in the study**

**Table 4: Profile of laboratory parameters of patients recruited in the study**

**Table 5: Complications of scrub typhus, numbers and percentages of patients.**

**Table 6: Comparison of characteristics of scrub typhus patients with controls with acute febrile illnesses**

**Table 7: Comparison of ANA during and 6 weeks after illness**

**Table 8: Bivariate analysis of ANA positivity with SOFA Day 1, 3 and 5, MODS and APACHE III scores**

**Table 9: Bivariate analysis of complications of scrub typhus and ANA positivity**

**Table 10: Bivariate analysis of individual parameters of SOFA D1 and ANA positivity**

**Table 11: Bivariate analysis of antinuclear antibody positivity and duration of hospital stay, duration of ICU stay and mortality in scrub typhus**

## ANNEXURE IV- STANDARD OPERATION PROTOCOL

### 1. THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE CALCULATED ON DAY 1, 3 AND 5 OF ADMISSION.

**Table 1.** The Sequential Organ Failure Assessment (SOFA) Score\*

Variables	SOFA Score				
	0	1	2	3	4
Respiratory PaO <sub>2</sub> /Fio <sub>2</sub> , mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets ×10 <sup>3</sup> /μL‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

\*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and Fio<sub>2</sub>, fraction of inspired oxygen.

†Values are with respiratory support.

‡To convert bilirubin from mg/dL to μmol/L, multiply by 17.1.

§Adrenergic agents administered for at least 1 hour (doses given are in μg/kg per minute).

||To convert creatinine from mg/dL to μmol/L, multiply by 88.4.



## 2. THE ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION (APACHE) III SCORING SYSTEM

**TABLE 1a**

APACHE III scoring system, comprised of the sum of three components: an acute physiology score, an age score, and a chronic health problems score. Scores range from 0 to 299 (physiology, 0 to 252; chronic health evaluation, 0 to 23; age, 0 to 24), with higher values representing a worse prognosis.

<b>Pulse</b>	8	5	0	1	5	7	13	17
	≤ 39	40-49	50-99	100-109	110-119	120-139	140-154	≥ 155
<b>Mean BP (mmHg)</b>	23	15	7	6	0	4	7	10
	≤ 39	40-59	60-69	70-79	80-99	100-119	120-129	≥ 130
<b>Temperature (°C)</b>	20	16	13	8	2	0	4	
	≤ 32.9	33-33.4	33.5-33.9	34-34.9	35-35.9	36-36.9	≥ 40	
<b>Respiratory Rate</b>	17	8	7	0	6	9	11	18
	≤ 5	6-11	12-13	14-24	25-34	35-39	40-49	≥ 50
<b>PaO<sub>2</sub>* (mmHg)</b>	15	5	2	0				
	≤ 49	50-69	70-79	≥ 80				
<b>AaDO<sub>2</sub>** (mmHg)</b>	0	7	9	11	14			
	< 100	100-249	250-349	350-499	≥ 500			
<b>Hematocrit (%)</b>	3	0	3					
	≤ 40.9	41-49	≥ 50					
<b>WBC Count (cu/mm) x 1000</b>	19	5	0	1	5			
	< 1.0	1.0-2.9	3.0-13.9	29-24.9	≥ 25			
<b>Serum Creatinine† (mg/dl) without ARF</b>	3	0	4	7				
	≤ 0.4	0.5-1.4	1.5-1.94	≥ 1.95				
<b>Serum Creatinine (mg/dl) with ARF</b>	0	10						
	0-1.4	≥ 1.5						
<b>Urine Output (cc/day)</b>	15	8	7	5	4	0	1	
	≤ 399	400-599	600-899	900-1499	1500-1999	2000-3999	≥ 4000	
<b>Serum BUN (mg/dl)</b>	0	2	7	11	12			
	≤ 16.9	17-19	20-39	40-79	≥ 80			
<b>Serum Na+ (mEq/L)</b>	3	2	0	4				
	≤ 119	120-134	135-154	≥ 155				
<b>Serum Albumin (g/dl)</b>	11	6	0	4				
	≤ 1.9	2.0-2.4	2.5-4.4	≥ 4.5				
<b>Serum Bilirubin (mg/dl)</b>	0	5	6	8	16			
	≤ 1.9	2.0-2.9	3.0-4.9	5.0-7.9	≥ 8.0			
<b>Serum Glucose (mg/dl)</b>	8	9	0	3	5			
	≤ 39	40-59	60-199	200-349	≥ 350			
<b>Age</b>	0	5	11	13	16	17	24	
	≤ 44	45-59	60-64	65-69	70-74	75-84	≥ 85	
<b>Comorbidities</b>	• AIDS 23 • Hepatic Failure 16 • Lymphoma 13 • Metastatic Cancer 11 • Leukemia/Multiple Myeloma 10 • Immune Compromised 10 • Cirrhosis 4							

**APACHE III**

was introduced to address some of the flaws of APACHE II. Although APACHE III resembles APACHE II, it includes new variables such as prior treatment location and the disease requiring ICU admission. In APACHE III scoring, the patient's age and chronic health history are worth up to 47 points. Within 24 hours of ICU admission, 17 physiologic variables are measured and may add up to a maximum of an additional 252 points. The resulting total score, in combination with prior treatment location and principal ICU diagnosis provides a predicted mortality.

**BENEFITS OF APACHE III:**

- Saves lives by better managing the care of critically ill individuals
- Reduces frequency of complications
- Evaluates and improves ICU performance
- Optimizes ICU resource allocation

**TABLE 1b**

APACHE III acute physiology scoring for neurologic abnormalities.

<b>Motor (Verbal) see †</b>	Oriented, Converses	Confused Conversation	Inappropriate Words & Incomprehensible Sounds	No Response
Obeys verbal command	0 / NA	3 / NA	10 / NA	15 / 16
Localizes pain	3 / NA	8 / NA	13 / NA	15 / 16
Flexion withdrawal/decoricate rigidity	3 / NA	13 / NA	24 / 24	24 / 33
Decerebrate rigidity/no response	3 / NA	13 / NA	29 / 29	29 / 48

TABLE 1a SCORE **a**

TABLE 1b SCORE **b**

TABLE 1c SCORE **c**

**APACHE III SCORE = a+b+c**

**TABLE 1c**

APACHE III acute physiology scoring for acid-base disturbances.

<b>Acute Physiology</b>	pCO <sub>2</sub> < 25	25 to < 30	30 to < 35	35 to < 40	40 to < 45	45 to < 50	50 to < 55	55 to < 60	pCO <sub>2</sub> ≥ 65
pH < 7.15	12							4	
7.15 to < 7.20	12							4	
7.20 to < 7.25	9	6		3			2		
7.25 to < 7.30		6		3			2		
7.30 to < 7.35	5	0			1				
7.35 to < 7.40		0			1				
7.40 to < 7.45	5	0			1				
7.45 to < 7.50		0			1				
7.50 to < 7.55	3	0			12				
7.55 to < 7.60		0			12				
7.60 to < 7.65	0	0			12				
pH ≥ 7.65		0			12				

† Scoring for Eyes open / do not open spontaneously or to painful/verbal stimulation  
 NA = Not applicable  
 \*If FIO<sub>2</sub> = 50%, record AaDO<sub>2</sub>; \*\* Alveolar-arterial Oxygen Difference; If FIO<sub>2</sub> < 50%, record PaO<sub>2</sub>.  
 †Acute renal failure (ARF) is defined as creatinine > 1.5 mg/dL and urine output < 400 cc/day and no chronic dialysis.  
 References: 1. Knaus WA et al. Chest 1991; 100(6):1619-1636. doi:10.1378/chest.100.6.1619  
 2. Ying-Chang C et al. Renal Failure 2002; 24(3): 285-96.

The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults.

W A Knaus; D P Wagner; E A Draper; J E Zimmerman; M Bergner; P G Bastos; C A Sirio; D J Murphy; T Lotring; A Damiano  
 Chest. 1991;100(6):1619-1636. doi:10.1378/chest.100.6.1619

## ANNEXURE V- DATA SHEET

finalANA thesis.s

1 : Risk\_Comorbid      M R

	Name	HospitalNo	AgeGroup	Age	Gender	Occupation	Location	Risk_Comorbid
1	Thulasi	604475F	1	22	2	4	1	M R
2	Vanmathi	604723F	3	50	2	4	1	nil
3	shajahan	623484F	3	57	1	4	1	nil
4	Shanti	611403F	2	35	2	3	1	nil
5	Venkatesan	611930F	3	66	1	1	1	HTN
6	Dasaratan	618746F	3	52	1	2	1	HTN
7	Mahabooba	623442F	2	35	2	4	2	nil
8	Sampath	618921F	2	36	1	3	3	nil
9	Kanchana	630681F	2	38	2	3	2	nil
10	Manjula	623849F	2	40	2	4	2	DM
11	Krishnamma	630468F	2	45	2	4	2	DM
12	Guralanar...	539524F	3	68	1	2	2	nil
13	Ramani	001642	4	74	2	4	1	HTN
14	Achammal	999978d	3	53	2	4	1	nil
15	Sarala	639512F	2	30	2	3	2	nil
16	Rajeshwari	955389C	3	61	2	4	1	HTN
17	Vasantha...	507937f	3	65	2	3	2	HTN
18	Vijayan	647312F	2	47	1	3	1	nil
19	Pushamma	646474F	2	38	2	4	2	nil
20	Padmavathi	297414d	1	28	2	4	3	nil
21	Venu	639491f	3	60	1	3	1	nil
22	Nirmala	646573F	1	28	2	4	1	nil
23	Valarmathi	651736f	2	35	2	4	3	DM
24	Ramesh	651630f	1	23	1	2	1	nil
25	Dasaratha...	651545F	3	65	1	4	2	nil

1 : Risk_Comorbid		M R						
	Name	HospitalNo	AgeGroup	Age	Gender	Occupation	Location	Risk_Comorbid
26	Teekaraman	651590F	2	43	1	3	1	nil
27	Mani	651738F	1	25	1	4	2	nil
28	Sivaranjini	651865F	1	19	2	4	3	Pregnancy
29	Devamma	651766F	3	58	2	3	1	nil
30	Prameela...	651827F	4	70	2	4	2	HTN
31	Saira Banu	657019F	1	25	2	4	1	Pregnancy
32	Varalakshmi	639799F	2	31	2	4	3	nil
33	Sk Farahad	646977F	2	39	2	4	2	DM
34	Kundagao...	657884F	1	17	1	3	2	Asthma
35	Gopinath	639794F	1	20	1	1	3	nil
36	Raghunad...	639795F	4	80	1	4	2	DM
37	Muthu	657779F	2	45	1	3	1	nil
38	Murugan	955062C	4	73	1	3	1	DM, HTN
39	Punitha	522157D	2	43	2	4	1	DM
40	Lokanadh...	657895F	3	51	1	3	2	nil
41	Suresh Ku...	657814F	2	31	1	3	1	nil
42	Kasiammal	338591F	4	71	2	4	1	DM
43	Vijaylaksh...	650322F	2	38	2	4	1	nil
44	Jalgadu Raja	657799F	2	32	1	3	2	nil
45	Prabakaran	657890F	1	26	1	3	1	nil
46	Bala Krish...	657769f	2	44	1	3	1	nil
47	Panjammal	639822F	4	82	2	4	1	nil
48	Jayaram R...	657675F	3	55	1	3	2	nil
49	Prabavathi	657650F	2	38	2	3	2	nil
50	Krishnaveni	639846F	3	63	2	4	1	HTN

1 : Risk_Comorbid		M R						
	Name	HospitalNo	AgeGroup	Age	Gender	Occupation	Location	Risk_Comorb id
51	Mandotiri	657690F	1	24	2	4	1	Pregnancy
52	Govindam...	651978F	4	75	2	4	2	HTN
53	Gangaiah	651933F	2	30	1	3	2	nil
54	Valarmathy	095895B	2	36	2	4	1	HIV
55	Kuppuswa...	639809F	4	70	1	4	1	nil
56	Bhaskar R...	664501F	4	72	1	4	2	nil
57	Venkatala...	657912F	2	45	2	4	3	nil
58	Sudhakar	670456F	3	57	1	3	2	nil
59	Bujamma	491258C	3	57	2	4	2	HIV
60	Mykal	657997F	2	32	1	2	3	nil
61	Chandra	664607F	1	20	2	4	2	nil
62	Munikann...	671514F	1	22	1	3	2	nil
63	Amalmary	671601F	3	63	2	2	1	nil
64	Sivasanmu...	664791F	2	40	1	3	1	DM, HTN
65	Kamalesan	671481F	2	45	1	3	1	nil
66	Murugaiyan	671712F	2	45	1	3	1	DM
67	Jayanti	671888F	2	42	2	4	1	nil
68	Singanam...	671589F	2	32	1	3	3	nil
69	Renammal	675874F	4	85	2	4	1	HTN
70	Poomani	329399D	3	50	2	4	2	HTN
71	Perumal	691285F	3	55	1	3	1	nil
72	Chandra	675699F	2	45	2	4	1	nil
73	Rangesh	675573F	3	55	1	3	1	nil
74	Samuel	675579F	2	33	1	3	1	nil
75	Jared	675477F	4	70	1	4	1	HTN

	Name	HospitalNo	AgeGroup	Age	Gender	Occupation	Location	Risk_Comorb id
76	Thenmozhi	675321F	1	25	2	3	1	nil
77	Andal	675316F	2	43	2	4	1	nil
78	Govindasa...	675274F	4	70	1	4	1	HTN
79	Dhanalaks...	675641F	2	44	2	4	2	nil
80	Saraswathi	264141B	2	37	2	4	1	DM
81	Panchalai	675876F	2	42	2	4	1	nil
82	Janaki	675667F	3	50	2	4	1	nil
83	Kaniyammal	675877F	3	55	2	4	1	HTN
84	Indirakanti	675875F	2	43	2	3	1	nil
85	Mercy	426570A	4	70	2	4	1	DM
86	Rajendran	750308F	2	40	1	3	1	nil
87	Janakiam...	751174F	3	63	2	4	1	DM
88	Devi	779868F	1	26	2	4	1	nil
89	Mohana	751493F	3	59	2	4	1	DM



1 : Fever 7

	Name	HospitalNo	Fever	Headache	NauseaVomiting	Rash	Cough	AlteredSensorium	Seizures	Myalgia	Abdominalpain	Breathlessness	Arthralgia	Jaundice	Oliguria	Bleeding
1	Thulasi	604475F	7	99	4	99	99	99	99	99	99	99	99	99	1	99
2	Vanmathi	604723F	5	99	99	99	5	99	99	5	99	5	99	99	1	99
3	shajahan	623484F	6	99	6	99	5	1	1	6	99	5	99	1	99	99
4	Shanti	611403F	7	99	1	99	99	99	99	99	1	3	99	99	3	99
5	Venkatesan	611930F	9	99	1	99	99	99	99	99	99	99	99	99	99	99
6	Dasaratan	618746F	10	7	7	99	5	99	99	5	99	5	5	99	99	99
7	Mahabooba	623442F	5	99	99	99	99	99	99	5	99	2	5	99	99	99
8	Sampath	618921F	13	99	99	99	7	99	99	7	99	99	99	99	99	99
9	Kanchana	630681F	7	7	1	99	99	1	99	7	7	99	99	99	99	99
10	Manjula	623849F	7	7	99	99	99	99	99	4	99	4	99	99	99	99
11	Krishnamma	630468F	7	7	7	99	99	99	99	99	99	99	5	99	99	99
12	Guralanar...	539524F	4	99	99	99	2	99	99	5	99	1	99	99	99	99
13	Ramani	001642	12	99	12	99	99	99	99	7	7	99	99	99	99	99
14	Achammal	999978d	8	99	99	99	99	1	99	99	8	1	99	99	99	99
15	Sarala	639512F	7	5	5	99	99	99	99	5	5	99	99	99	99	99
16	Rajeshwari	955389C	10	5	5	99	5	99	99	5	5	99	99	99	99	99
17	Vasantha...	507937f	10	99	99	99	5	99	99	5	5	6	99	99	99	99
18	Vijayan	647312F	3	99	7	99	99	99	99	99	7	7	99	99	99	99
19	Pushamma	646474F	4	99	99	99	4	99	99	4	4	2	4	99	99	99
20	Padmavathi	297414d	15	15	99	99	10	99	99	15	99	99	99	99	99	99
21	Venu	639491f	10	99	99	99	99	99	99	99	99	2	99	99	99	99
22	Nirmala	646573F	7	7	7	99	99	99	99	7	99	7	99	99	99	99
23	Valarmathi	651736f	3	99	3	99	99	99	99	3	99	99	99	99	99	99
24	Ramesh	651630f	3	3	1	99	99	99	99	3	3	99	99	99	99	99
25	Dasaratha...	651545F	5	99	99	99	99	99	99	5	5	5	99	99	99	99

'6 : Name Teekaraman

	Name	Hospitalno	Fever	Headache	NauseaVomiting	Rash	Cough	AlteredSensurium	Seizures	Myalgia	Abdominalpain	Breathlessness	Arthralgia	Jaundice	Oliguria	Bleeding
26	Teekaraman	651590F	10	99	3	99	3	99	99	99	3	99	99	99	99	99
27	Mani	651738F	10	10	99	99	99	99	99	9	99	99	99	99	99	99
28	Sivaranjini	651865F	5	99	99	99	3	99	99	99	99	3	99	99	3	99
29	Devamma	651766F	10	7	5	99	99	1	99	7	99	99	99	99	99	99
30	Prameela...	651827F	10	99	99	5	99	99	99	99	99	5	99	99	99	99
31	Saira Banu	657019F	14	99	99	99	99	99	99	99	99	99	99	99	99	99
32	Varalakshmi	639799F	7	99	99	99	5	99	99	99	99	3	99	99	99	99
33	Sk Farahad	646977F	15	99	99	99	99	99	99	15	99	3	99	99	99	99
34	Kundagao...	657884F	7	7	7	99	99	99	99	99	99	99	99	99	99	99
35	Gopinath	639794F	7	99	7	99	99	99	99	5	5	99	5	99	99	99
36	Raghunad...	639795F	7	99	2	99	99	99	99	99	99	99	99	99	99	99
37	Muthu	657779F	10	7	99	99	99	99	99	99	99	7	99	99	99	99
38	Murugan	955062C	4	99	3	99	99	99	99	99	99	99	99	99	99	99
39	Punitha	522157D	8	99	4	99	99	99	99	99	99	99	99	99	99	99
40	Lokanadh...	657895F	2	2	2	99	99	99	99	2	99	99	99	99	99	99
41	Suresh Ku...	657814F	15	99	99	99	99	99	99	10	99	99	99	10	99	99
42	Kasiammal	338591F	7	99	7	99	99	99	99	7	99	99	99	99	99	99
43	Vijaylaksh...	650322F	5	5	5	99	99	99	99	5	99	99	99	99	99	99
44	Jal gadu Raja	657799F	15	2	2	99	99	99	99	99	99	99	99	99	99	99
45	Prabakaran	657890F	10	99	4	4	99	99	99	10	4	1	99	3	99	99
46	Bala Krish...	657769F	7	3	99	99	99	1	99	99	99	99	99	99	99	99
47	Panjammal	639822F	10	99	99	99	99	99	99	99	99	2	99	99	99	99
48	Jayaram R...	657675F	7	99	99	99	99	99	99	5	99	99	99	99	99	99
49	Prabavathi	657650F	10	1	1	99	99	99	99	99	99	99	99	99	99	99
50	Krishnaveni	639846F	2	99	99	99	99	99	99	99	99	1	99	99	99	99

26 : Name		Teekaraman														
	Name	Hospitalno	Fever	Headache	NauseaVomiting	Rash	Cough	AlteredSensorium	Seizures	Myalgia	Abdominalpain	Breathlessness	Arthralgia	Jaundice	Oliguria	Bleeding
51	Mandotiri	657690F	9	9	99	99	99	99	99	99	99	3	99	99	99	99
52	Govindam...	651978F	10	99	99	99	99	99	99	10	99	99	99	99	99	99
53	Gangaiah	651933F	5	1	99	99	1	99	99	99	99	1	99	99	99	99
54	Valarmathy	095895B	7	5	5	99	99	99	99	5	99	99	99	99	99	99
55	Kuppuswa...	639809F	2	2	99	99	99	99	99	99	99	99	99	99	99	99
56	Bhaskar R...	664501F	10	99	99	99	99	1	99	99	99	99	99	99	99	99
57	Venkatala...	657912F	7	99	3	99	99	99	99	99	3	3	99	99	99	99
58	Sudhakar	670456F	14	99	2	99	99	99	99	99	99	99	99	14	99	99
59	Bujamma	491258C	10	4	2	99	99	99	99	99	99	4	99	99	99	99
60	Mykal	657997F	10	99	4	99	99	2	1	4	99	99	99	4	99	99
61	Chandra	664607F	10	8	2	99	99	99	99	2	99	99	2	99	99	99
62	Munikann...	671514F	10	99	99	99	99	99	99	99	99	5	99	99	99	99
63	Amalmary	671601F	12	4	99	99	99	99	99	4	99	4	99	99	99	99
64	Sivasanmu...	664791F	4	4	4	99	99	99	99	4	99	4	99	99	99	99
65	Kamalesan	671481F	4	99	99	99	99	99	99	4	99	99	99	99	99	99
66	Murugaiyan	671712F	5	99	5	99	99	99	99	5	5	3	99	99	99	99
67	Jayanti	671888F	10	10	99	99	99	99	99	99	99	5	99	5	99	99
68	Singanam...	671589F	4	99	3	99	99	99	99	99	3	3	99	99	99	99
69	Renammal	675874F	7	7	99	99	3	99	99	7	99	3	99	99	1	99
70	Poomani	329399D	15	15	7	99	4	99	99	15	7	4	99	99	2	99
71	Perumal	691285F	8	99	99	99	99	99	99	99	99	8	99	99	99	99
72	Chandra	675699F	7	5	3	99	99	99	99	7	3	5	99	99	99	99
73	Rangesh	675573F	12	99	99	99	99	99	99	12	99	99	99	99	99	99
74	Samuel	675579F	10	7	99	99	2	99	99	7	99	2	99	99	99	99
75	Jared	675477F	2	1	99	99	99	99	99	1	99	99	99	99	99	99

1 : Fever		7														
	Name	Hospitalno	Fever	Headache	NauseaVomiting	Rash	Cough	AlteredSensorium	Seizures	Myalgia	Abdominalpain	Breathlessness	Arthralgia	Jaundice	Oliguria	Bleeding
76	Thenmozhi	675321F	10	99	5	99	8	99	99	10	5	8	99	99	99	99
77	Andal	675316F	4	99	3	99	99	99	99	99	99	3	99	99	99	99
78	Govindasa...	675274F	4	99	1	99	99	1	99	4	99	4	99	99	99	99
79	Dhanalaks...	675641F	5	5	99	99	99	99	99	5	99	99	99	99	99	99
80	Saraswathi	264141B	10	99	99	99	2	99	99	99	99	2	99	99	99	99
81	Panchalai	675876F	4	99	4	99	99	99	99	4	4	99	99	99	99	99
82	Janaki	675667F	7	99	5	99	99	99	99	7	5	5	99	99	99	99
83	Kaniyammal	675877F	4	99	99	99	99	99	99	4	99	2	99	99	99	99
84	Indirakanti	675875F	7	7	99	99	2	99	99	99	99	2	99	99	99	99
85	Mercy	426570A	7	5	5	99	99	99	99	99	99	2	99	99	99	99
86	Rajendran	750308F	7	7	99	99	99	99	99	7	99	1	99	99	1	99
87	Janakiam...	751174F	7	99	99	99	2	99	99	99	99	2	99	99	99	99
88	Devi	779868F	7	99	99	99	4	99	99	2	99	2	99	99	99	99
89	Mohana	751493F	8	99	99	99	8	99	99	99	99	8	99	99	99	99



1 : Name		Thulasi																	Visible: 84 of t	
	Name	Hospitalno	Pallor	Icterus	Lymphadenopathy	Rashsign	Oedema	Eschar	Tachycardia	SpO2	Tachypnoea	Hypotension	Feversign	Hepatomegaly	Splenomegaly	Petechiae	Creptitations	AlteredSenseSign	NeckStiffn...	
1	Thulasi	604475F	1	0	0	0	0	1	1	86	1	0	1	0	0	0	0	0	0	
2	Vanmathi	604723F	0	0	0	0	0	1	1	88	1	1	1	1	0	0	1	0	0	
3	shajahan	623484F	0	1	0	0	0	1	1	96	1	1	0	1	1	0	1	1	0	
4	Shanti	611403F	0	0	0	0	0	0	1	93	1	1	0	1	0	0	1	0	0	
5	Venkatesan	611930F	0	1	0	0	0	1	1	93	1	0	0	1	1	0	1	0	0	
6	Dasaratan	618746F	1	0	0	0	0	1	1	96	1	0	1	0	1	0	1	0	0	
7	MahaBooba	623442F	1	0	0	0	0	1	0	97	1	0	1	1	1	0	1	0	0	
8	Sampath	618921F	0	1	0	0	0	1	1	89	1	0	1	1	1	0	0	0	0	
9	Kanchana	630681F	1	0	0	0	0	1	1	99	1	1	0	0	0	0	0	1	0	
10	Manjula	623849F	0	1	0	0	0	1	1	90	1	0	0	0	0	0	1	0	0	
11	Krishnamma	630468F	1	0	0	0	0	1	0	98	0	0	0	0	0	0	0	0	0	
12	Guralanar...	539524F	0	0	0	0	0	1	1	99	1	1	0	1	0	0	1	0	0	
13	Ramani	001642	0	0	0	0	0	1	1	99	0	0	0	0	0	0	0	0	0	
14	Achammal	999978d	1	0	0	0	0	1	1	78	1	0	1	0	0	0	0	1	0	
15	Sarala	639512F	0	0	0	0	0	0	1	94	1	0	1	1	1	0	0	0	0	
16	Rajeshwari	955389C	0	0	0	0	0	0	1	99	0	0	1	0	0	0	0	0	0	
17	Vasantha...	507937F	1	0	0	0	0	1	1	93	1	0	1	0	0	0	1	0	0	
18	Vijayan	647312F	0	0	0	0	0	1	0	96	1	0	0	0	1	0	1	0	0	
19	Pushamma	646474F	0	1	1	0	0	0	1	98	1	0	0	0	0	0	1	0	0	
20	Padmavathi	297414d	1	0	0	0	0	1	1	95	0	1	1	1	1	0	0	0	0	
21	Venu	639491f	0	0	0	0	0	1	1	94	1	0	0	0	0	0	1	0	0	
22	Nirmala	646573F	0	0	0	0	0	0	0	97	1	1	0	0	0	0	0	0	0	
23	Valarmathi	651736f	0	0	0	0	0	0	1	96	1	0	0	0	0	0	0	0	0	
24	Ramesh	651630f	0	0	0	0	0	1	0	98	0	0	0	0	0	0	0	0	0	
25	Dasaratha...	651545F	0	0	0	0	0	1	1	98	1	0	0	0	0	0	1	0	0	

1 : Pallor		1																	Visible: 84 of	
	Name	Hospitalno	Pallor	Icterus	Lymphadenopathy	Rashsign	Oedema	Eschar	Tachycardia	SpO2	Tachypnoea	Hypotension	Feversign	Hepatomegaly	Splenomegaly	Petechiae	Creptitations	AlteredSenseSign	NeckStiffn...	
26	Teekaraman	651590F	0	0	0	0	0	1	1	95	1	0	1	0	0	0	1	0	0	
27	Mani	651738F	0	0	0	0	0	1	1	93	0	0	1	0	0	0	0	0	0	
28	Sivaranjini	651865F	0	0	0	0	1	1	0	93	1	0	1	0	0	0	1	0	0	
29	Devamma	651766F	1	1	0	0	1	1	1	86	1	0	0	1	0	0	1	0	1	
30	Prameela...	651827F	1	0	0	0	1	1	0	98	1	0	0	0	0	0	1	0	0	
31	Saira Banu	657019F	1	0	0	0	0	1	1	92	1	0	0	0	0	0	1	0	0	
32	Varalakshmi	639799F	0	0	0	0	0	0	1	90	1	0	0	0	0	0	0	0	0	
33	Sk Farahad	646977F	1	0	0	0	0	1	1	87	1	0	1	0	0	0	1	0	0	
34	Kundagao...	657884F	0	0	0	0	0	1	1	97	1	0	0	0	0	0	0	0	0	
35	Gopinath	639794F	0	0	0	0	0	1	0	98	0	0	1	0	1	0	0	0	0	
36	Raghunad...	639795F	0	0	0	0	0	1	1	97	1	0	1	0	0	0	0	0	0	
37	Muthu	657779F	0	0	0	0	0	1	1	98	1	1	1	0	0	0	0	0	0	
38	Murugan	955062C	0	0	0	0	0	0	1	98	1	0	1	0	0	0	0	0	0	
39	Punitha	522157D	0	0	0	0	0	1	1	98	1	1	0	0	0	0	0	0	0	
40	Lokanadh...	657895F	0	0	0	0	0	0	1	97	1	0	0	0	0	0	0	0	0	
41	Suresh Ku...	657814F	0	1	0	0	1	0	1	95	1	0	1	1	1	0	1	0	0	
42	Kasiammal	338591F	0	0	0	0	0	0	0	98	1	0	0	0	0	0	0	0	0	
43	Vijaylaksh...	650322F	0	0	0	0	0	0	0	98	0	0	0	0	0	0	0	0	0	
44	Jalgadu Raja	657799F	0	0	0	0	0	0	0	98	1	0	0	0	0	0	0	0	0	
45	Prabakaran	657890F	0	1	0	1	0	0	1	93	1	0	0	1	1	0	0	0	0	
46	Bala Krish...	657769f	0	0	0	0	0	1	1	98	1	0	0	0	0	0	0	1	0	
47	Panjammal	639822F	0	0	0	0	0	1	1	96	1	0	0	0	0	0	1	0	0	
48	Jayaram R...	657675F	0	0	0	0	0	1	0	94	1	0	0	0	0	0	0	0	0	
49	Prabavathi	657650F	0	0	0	0	0	1	1	96	1	1	0	0	0	0	1	0	0	
50	Krishnaveni	639846F	0	0	0	0	0	0	1	98	1	0	0	0	0	0	1	0	0	

1 : Pallor 1 Visible: 84 of

	Name	HospitalNo	Pallor	Icterus	Lymphadeno pathy	Rashsign	Oedema	Eschar	Tachycardia	SpO2	Tachypnoea	Hypotension	Feversign	Hepatomegaly	Splenomegaly	Petechiae	Crepitations	AlteredSense Sign	NeckStiffn...
51	Mandotiri	657690F	0	0	0	0	0	1	1	95	1	1	1	0	0	0	1	0	0
52	Govindam...	651978F	0	0	0	0	0	0	0	90	1	0	0	0	0	0	1	0	0
53	Gangaiah	651933F	0	0	0	0	0	1	1	98	0	0	0	0	0	0	1	0	0
54	Valarmathy	095895B	0	0	0	0	0	0	1	97	1	0	1	0	0	0	0	0	0
55	Kuppuswa...	639809F	0	0	0	0	0	0	0	96	0	0	0	0	0	0	0	0	1
56	Bhaskar R...	664501F	0	0	0	0	0	1	1	95	1	0	0	0	0	0	0	1	1
57	Venkatala...	657912F	1	0	0	0	1	1	1	75	1	0	0	0	0	0	1	0	0
58	Sudhakar	670456F	1	1	0	0	1	1	1	98	1	0	1	0	0	0	0	0	0
59	Bujamma	491258C	0	0	0	0	0	1	1	94	1	1	1	0	0	0	1	0	0
60	Mykal	657997F	0	1	0	1	0	0	0	92	1	0	0	1	1	0	0	1	0
61	Chandra	664607F	0	1	0	0	1	0	1	97	0	0	0	1	0	0	0	0	0
62	Munikann...	671514F	0	0	0	0	0	1	1	90	1	0	0	0	0	0	1	0	0
63	Amalarnary	671601F	0	0	0	0	0	1	1	93	1	0	0	0	0	0	1	0	0
64	Sivasanmu...	664791F	0	0	0	0	1	1	1	95	1	1	0	0	0	0	1	0	0
65	Kamalesan	671481F	0	0	0	0	0	1	1	99	0	0	0	0	0	0	0	0	0
66	Murugaiyan	671712F	0	1	0	0	0	0	1	93	1	0	0	0	0	0	1	0	0
67	Jayanti	671888F	0	1	0	0	0	1	1	94	1	0	0	1	1	0	1	0	0
68	Singanam...	671589F	0	1	0	0	0	1	1	35	1	0	0	0	1	0	1	0	0
69	Renammal	675874F	0	0	0	0	0	1	0	74	1	0	0	0	0	0	1	0	0
70	Poomani	329399D	0	0	0	0	0	1	1	90	1	0	0	0	0	0	1	0	0
71	Perumal	691285F	0	0	0	0	0	1	1	88	1	1	1	0	0	0	1	0	0
72	Chandra	675699F	0	0	0	0	0	1	1	94	0	0	0	0	0	0	1	0	0
73	Rangesh	675573F	0	0	0	0	0	1	1	91	0	0	1	0	0	0	0	0	0
74	Samuel	675579F	0	1	0	0	0	1	1	90	1	0	1	0	0	0	1	0	0
75	Jared	675477F	0	0	0	0	0	1	1	94	0	0	1	0	0	0	0	0	0

1 : Pallor 1 Visible: 84 of

	Name	HospitalNo	Pallor	Icterus	Lymphadeno pathy	Rashsign	Oedema	Eschar	Tachycardia	SpO2	Tachypnoea	Hypotension	Feversign	Hepatomegaly	Splenomegaly	Petechiae	Crepitations	AlteredSense Sign	NeckStiffn...
76	Thenmozhi	675321F	0	0	0	0	0	1	1	94	1	1	0	0	0	0	1	0	0
77	Andal	675316F	0	0	0	0	0	1	0	94	1	1	0	0	0	0	1	0	0
78	Govindasa...	675274F	0	0	0	0	0	1	1	94	0	0	0	0	0	0	1	1	1
79	Dhanalaks...	675641F	0	0	0	0	0	1	1	94	1	1	1	0	0	0	1	0	0
80	Saraswathi	264141B	0	0	0	0	1	1	1	98	1	0	0	0	0	0	1	0	0
81	Panchalai	675876F	1	1	0	0	0	1	1	94	0	0	0	1	0	0	0	0	0
82	Janaki	675667F	0	0	0	0	0	1	1	88	1	0	1	0	0	0	1	0	0
83	Kaniyammal	675877F	1	0	0	0	0	1	1	89	1	1	1	0	0	0	1	0	0
84	Indirakanti	675875F	0	0	0	0	0	1	1	93	1	1	0	0	0	0	1	0	0
85	Mercy	426570A	0	0	0	0	0	1	1	89	1	0	0	0	0	0	1	0	0
86	Rajendran	750308F	0	0	0	0	0	1	1	81	1	0	1	0	0	0	1	0	0
87	Janakiam...	751174F	1	0	0	0	0	1	1	84	1	0	0	0	0	0	1	0	0
88	Devi	779868F	0	0	0	0	0	1	1	97	1	0	0	0	0	0	1	0	0
89	Mohana	751493F	0	0	0	0	0	1	1	57	1	0	0	0	0	0	1	0	0

1 : Name		Thulasi																		Visible: 66 of 66 Variabl	
	Name	Hospitalno	Hb	TLC	NeutrophilPercent	Platelets	Creatinine	Sodium	Potassium	Bicarbonate	CPK	TotalBilirubin	DirectBilirubin	Protein	Albumin	SGOT	SGPT	ALP	Chestinfiltrates	ANA	
1	Thulasi	604475F	14.2	4400	59.0	50000	2.94	157.00	4.30	16.00	99.0	.5	.1	7.9	3.70	570	189	370	0	4	
2	Vanmathi	604723F	14.7	10600	83.0	75000	1.44	131.00	3.10	21.00	99.0	1.3	.6	4.7	2.10	159	62	105	1	2	
3	shajahan	623484F	14.1	14100	39.0	67000	4.73	115.00	4.73	10.00	707.0	7.1	4.7	5.1	2.20	245	109	248	1	2	
4	Shanti	611403F	12.4	5900	81.0	38000	1.54	133.00	3.20	21.00	99.0	1.1	.7	5.6	2.50	133	67	129	1	0	
5	Venkatesan	611930F	13.2	13700	87.0	41000	3.04	137.00	3.60	8.30	81.0	5.3	4.6	6.3	3.10	69	110	195	1	2	
6	Dasaratan	618746F	8.8	10000	74.0	126000	1.32	136.00	3.30	17.00	99.0	.7	.5	6.1	2.50	85	55	152	1	2	
7	Mahabooba	623442F	8.5	10100	85.0	67000	.99	134.00	3.40	23.00	99.0	3.5	2.9	6.2	2.40	152	62	162	0	2	
8	Sampath	618921F	11.5	9400	61.0	55000	1.18	125.00	4.40	21.00	99.0	4.7	2.5	6.0	2.30	126	88	290	0	2	
9	Kanchana	630681F	9.7	6200	76.0	23000	1.23	140.00	3.70	20.00	5313.0	3.5	2.8	5.2	1.90	604	181	270	0	0	
10	Manjula	623849F	11.8	11500	83.0	63000	.92	137.00	3.00	15.30	99.0	6.4	4.5	8.3	3.20	91	27	408	1	1	
11	Krishnamma	630468F	10.0	14500	96.0	9000	1.78	118.00	2.50	18.00	38.0	1.0	.6	7.1	2.90	159	159	120	0	0	
12	Guralanar...	539524F	14.6	6600	63.0	38000	.89	135.00	4.20	18.00	155.0	4.3	2.9	5.3	2.00	233	113	617	1	1	
13	Ramani	001642	11.8	15600	60.0	192000	.81	127.00	5.60	18.60	99.0	.8	.3	7.1	3.20	144	92	186	0	0	
14	Achammal	999978d	8.6	20100	60.0	27000	1.38	137.00	3.80	15.90	99.0	4.2	3.0	5.1	2.20	77	20	468	1	0	
15	Sarala	639512F	9.5	8100	66.0	95000	.69	129.00	2.90	26.00	99.0	1.8	.9	6.7	1.90	136	134	189	0	4	
16	Rajeshwari	955389C	12.7	6100	73.0	156000	1.85	135.00	4.90	17.00	99.0	.6	.3	8.2	4.30	245	224	133	0	4	
17	Vasantha...	507937F	11.2	11200	53.0	5000	.66	137.00	3.80	20.00	63.0	.4	.2	6.0	2.90	61	39	87	1	0	
18	Vijayan	647312F	12.8	16600	63.0	45000	2.82	126.00	4.50	21.00	99.0	7.0	5.7	5.7	2.70	180	146	191	1	4	
19	Pushamma	646474F	12.8	9600	72.0	54000	1.03	130.00	4.70	24.00	99.0	4.0	3.4	6.4	2.70	101	55	304	1	1	
20	Padmavathi	297414d	9.9	9300	58.0	85000	.77	130.00	3.50	19.00	99.0	2.9	2.5	5.9	2.50	206	180	294	0	4	
21	Venu	639491F	14.0	7600	59.0	90000	1.29	135.00	4.00	17.00	99.0	.8	.4	6.6	2.70	254	94	96	1	2	
22	Nirmala	646573F	12.7	18300	78.0	169000	1.50	135.00	3.70	19.00	99.0	1.0	.9	5.6	2.40	114	106	154	0	4	
23	Valarmathi	651736F	13.8	8100	67.0	107000	.90	133.00	3.50	15.10	99.0	1.0	.5	6.7	3.20	129	121	121	0	1	
24	Ramesh	651630F	15.2	12800	80.0	120000	1.18	130.00	3.70	24.00	24.0	1.2	.1	7.7	3.80	57	51	101	0	0	
25	Dasaratha...	651545F	11.1	7300	84.0	18000	1.25	135.00	3.60	19.00	99.0	5.2	4.8	5.7	2.70	154	81	163	1	4	

1 : Name		Thulasi																		Visible: 66 of 66 Variabl	
	Name	Hospitalno	Hb	TLC	NeutrophilPercent	Platelets	Creatinine	Sodium	Potassium	Bicarbonate	CPK	TotalBilirubin	DirectBilirubin	Protein	Albumin	SGOT	SGPT	ALP	Chestinfiltrates	ANA	
26	Teekaraman	851590F	12.6	10000	73.0	33000	1.51	123.00	4.30	17.00	99.0	.3	.2	6.9	2.80	113	61	109	0	0	
27	Mani	651738F	16.1	8700	61.0	123000	1.28	134.00	4.20	21.00	99.0	.9	.6	6.9	3.60	149	197	152	0	0	
28	Sivaranjini	651865F	10.4	20400	87.0	24000	.86	134.00	3.10	20.20	99.0	.6	.3	5.5	2.20	71	29	115	1	2	
29	Devamma	651766F	8.0	10100	92.0	69000	2.35	136.00	3.40	19.00	99.0	3.4	3.1	5.9	2.60	111	73	443	1	0	
30	Prameela...	651827F	8.4	4700	57.0	10000	1.46	140.00	4.20	29.00	99.0	.4	.3	5.8	2.20	110	66	168	0	1	
31	Saira Banu	657019F	9.6	11100	65.0	118000	1.00	134.00	3.50	22.00	99.0	.4	.2	5.5	2.40	47	10	181	1	4	
32	Varalakshmi	639799F	10.2	11200	66.0	31000	.76	135.00	3.60	21.80	99.0	.9	.7	6.0	2.50	52	51	161	0	1	
33	Sk Farahad	646977F	8.0	18500	48.0	109000	1.12	137.00	3.50	16.00	99.0	.6	.5	6.5	2.70	57	71	233	0	0	
34	Kundagao...	657884F	13.7	6700	89.0	76000	1.03	137.00	3.90	22.00	99.0	.7	.4	6.4	3.60	259	574	109	0	4	
35	Gopinath	639794F	14.2	10600	70.0	5000	1.31	134.00	3.70	19.00	99.0	.8	.1	6.8	3.90	155	87	103	0	0	
36	Raghunad...	639795F	11.4	9500	78.0	134000	1.14	119.00	3.40	21.00	99.0	.9	.6	6.7	2.90	177	120	98	0	4	
37	Muthu	657779F	14.1	10900	76.0	5000	1.22	128.00	3.30	24.30	99.0	1.3	.6	8.0	3.50	86	84	138	0	1	
38	Murugan	955062C	12.7	5000	87.0	79000	1.15	131.00	3.90	17.60	99.0	.8	.3	6.5	3.30	97	45	57	0	0	
39	Punitha	522157D	10.6	13500	86.0	80000	2.45	125.00	3.80	11.60	99.0	.6	.5	6.6	3.10	162	77	77	0	4	
40	Lokanadh...	657895F	11.9	7800	82.0	129000	1.60	136.00	3.70	17.00	1500.0	.7	.4	7.0	3.70	100	66	122	0	4	
41	Suresh Ku...	657814F	12.1	13500	83.0	251000	.97	131.00	3.50	21.00	99.0	1.9	1.7	6.8	2.60	317	133	113	0	2	
42	Kasiammal	338591F	9.0	15500	83.0	290000	.97	134.00	2.40	28.00	99.0	.9	.3	6.7	2.70	86	57	213	0	1	
43	Vijaylaksh...	650322F	13.3	7300	68.0	225000	.87	129.00	3.50	24.00	99.0	.4	.2	7.3	4.10	34	33	42	0	1	
44	JalgaDu Raja	657799F	14.4	13500	66.0	243000	1.64	130.00	3.90	20.00	99.0	.7	.4	6.6	3.70	63	102	131	0	1	
45	Prabakaran	657890F	11.3	16100	60.0	91000	.61	137.00	3.30	22.00	99.0	11.4	9.8	6.1	2.30	335	160	445	0	4	
46	Bala Krish...	657769F	13.0	5500	74.0	125000	1.50	128.00	3.00	22.00	99.0	.9	.7	8.3	3.80	162	129	138	0	4	
47	Panjammal	639822F	11.4	19800	91.0	87000	1.45	129.00	4.00	12.00	99.0	1.2	.8	6.6	2.60	91	35	183	1	2	
48	Jayaram R...	657675F	13.9	11000	89.0	7000	1.04	120.00	4.50	20.00	99.0	.8	.4	7.2	3.20	46	23	133	0	1	
49	Prabavathi	657650F	11.1	10400	63.0	23000	1.00	137.00	3.70	18.00	99.0	1.0	.9	6.5	2.80	142	93	152	0	4	
50	Krishnaveni	639846F	13.3	9300	67.0	186000	2.33	134.00	3.60	16.00	99.0	.6	.2	8.3	3.90	351	199	187	1	4	

1 : Name		Thulasi																		Visible: 66 of 66 Variat	
	Name	Hospitalno	Hb	TLC	NeutrophilPercent	Platelets	Creatinine	Sodium	Potassium	Bicarbonate	CPK	TotalBiliru...	DirectBilirubin	Protein	Albumin	SCOT	SGPT	ALP	Chestinfiltrates	ANA	
51	Mandotiri	657690F	11.1	8700	80.0	47000	.72	130.00	3.50	20.10	99.0	.5	.3	5.8	3.00	180	142	114	1	0	
52	Govindam...	651978F	12.5	9700	82.0	51000	1.02	138.00	4.00	22.00	99.0	.7	.6	6.7	2.60	123	41	225	1	1	
53	Gangaiah	651933F	12.4	10500	84.0	89000	1.11	133.00	3.50	19.00	99.0	.6	.5	6.0	2.80	104	60	136	0	4	
54	Valarmathy	095895B	12.7	7600	53.0	173000	.83	132.00	3.80	21.00	99.0	.2	.1	7.3	3.50	60	37	165	0	0	
55	Kuppuswa...	639809F	13.5	12100	86.0	160000	3.15	142.00	3.70	18.00	99.0	.	.	.	.	148	82	.	0	1	
56	Bhaskar R...	664501F	13.8	9900	94.0	150000	4.50	131.00	3.70	11.00	99.0	3.3	3.0	6.9	2.70	65	51	173	0	2	
57	Venkatala...	657912F	9.1	12800	67.0	7000	1.43	134.00	4.40	16.70	99.0	2.6	2.1	4.8	1.40	103	33	358	1	2	
58	Sudhakar	670456F	7.9	4300	85.0	55000	1.20	123.00	3.70	18.20	99.0	1.5	1.2	6.2	2.90	116	38	184	1	1	
59	Bujamma	491258C	11.7	8300	87.0	31000	1.00	126.00	3.80	18.00	99.0	2.0	1.5	5.4	2.80	158	78	110	1	4	
60	Mykal	657997F	12.4	11300	77.0	116000	.66	135.00	4.10	20.40	99.0	5.4	4.9	7.1	3.10	161	128	232	0	1	
61	Chandra	664607F	9.5	9800	72.0	18000	.57	139.00	3.90	23.00	99.0	9.9	8.5	5.9	2.30	208	49	220	0	1	
62	Munikann...	671514F	12.3	10100	44.0	113000	.92	136.00	3.80	25.00	99.0	.3	.1	5.8	2.40	174	58	106	1	2	
63	Amalamy	671601F	10.1	7800	68.0	50000	1.70	130.00	4.10	21.00	99.0	.4	.3	6.0	2.80	90	130	172	1	2	
64	Sivasanm...	664791F	13.2	9700	66.0	83000	1.67	119.00	4.20	14.00	404.0	1.0	.2	6.5	2.80	110	59	111	1	2	
65	Kamalesan	671481F	12.4	10500	80.0	105000	1.20	123.00	4.00	22.00	99.0	2.6	2.0	6.2	2.80	128	61	369	0	1	
66	Murugaiyan	671712F	13.2	11200	87.0	9000	3.19	122.00	3.90	16.00	99.0	6.4	5.7	5.8	2.10	62	63	330	1	0	
67	Jayanti	671888F	11.9	5500	72.0	72000	1.02	125.00	3.50	18.00	99.0	7.2	6.5	6.3	2.50	306	78	135	1	2	
68	Singanam...	671589F	16.5	22700	63.0	10000	1.21	131.00	3.80	18.00	99.0	3.7	2.8	6.0	2.60	505	200	250	1	1	
69	Renammal	675874F	11.1	8900	76.0	168000	2.09	139.00	4.50	30.00	99.0	.3	.1	6.5	3.40	48	21	67	1	4	
70	Poomani	329399D	11.1	11000	81.0	117000	.92	137.00	4.00	25.00	99.0	1.3	1.0	5.9	2.70	77	57	225	1	0	
71	Perumal	691285F	14.3	6300	71.0	82000	1.80	145.00	5.10	9.40	99.0	1.3	.9	4.8	1.70	111	65	43	1	2	
72	Chandra	675699F	11.4	13300	69.0	7000	.93	130.00	3.30	21.00	99.0	1.0	.2	6.7	2.60	112	73	100	1	2	
73	Rangesh	675573F	12.9	15500	74.0	199000	1.19	125.00	5.00	25.00	99.0	1.3	.8	7.2	3.10	114	45	266	0	3	
74	Samuel	675579F	12.9	10000	84.0	83000	1.05	133.00	4.00	20.00	99.0	7.9	6.2	6.1	3.00	105	60	96	1	4	
75	Jared	675477F	14.7	14500	90.0	22000	1.50	130.00	3.40	23.00	99.0	1.4	1.0	5.9	2.60	214	82	101	0	2	

1 : Name		Thulasi																		Visible: 66 of 66 Varia	
	Name	Hospitalno	Hb	TLC	NeutrophilPercent	Platelets	Creatinine	Sodium	Potassium	Bicarbonate	CPK	TotalBiliru...	DirectBilirubin	Protein	Albumin	SCOT	SGPT	ALP	Chestinfiltrates	ANA	
76	Thenmozhi	675321F	11.7	8300	58.0	51000	1.32	134.00	3.50	22.00	33.0	.4	.2	5.7	2.20	148	75	153	1	2	
77	Andal	675316F	10.3	14200	79.0	115000	1.41	130.00	4.30	12.30	99.0	.4	.2	6.4	2.30	70	26	100	1	3	
78	Govindasa...	675274F	11.6	18700	75.0	70000	4.98	134.00	4.50	16.00	99.0	6.4	4.6	5.2	2.20	89	61	103	1	2	
79	Dhanalak...	675641F	10.8	12900	66.0	36000	1.65	126.00	3.60	21.00	99.0	1.1	.5	5.1	2.60	100	70	151	1	1	
80	Saraswathi	264141B	12.2	10500	72.0	19000	1.26	124.00	4.30	14.00	99.0	1.1	1.0	6.4	2.80	50	36	124	1	2	
81	Panchalai	675876F	9.2	16000	36.0	94000	1.24	136.00	3.70	17.00	99.0	6.3	4.4	5.9	1.60	294	211	568	0	0	
82	Janaki	675667F	11.8	13200	84.0	34000	.86	133.00	4.00	26.00	99.0	.9	.6	6.4	3.20	76	55	175	1	1	
83	Kaniyammal	675877F	9.5	7000	55.0	55000	1.97	137.00	4.00	17.00	99.0	3.4	3.0	6.9	2.90	35	20	261	1	1	
84	Indirakanti	675875F	11.2	10600	71.0	4000	2.19	122.00	3.20	16.00	99.0	2.4	1.9	5.8	2.30	340	96	149	1	1	
85	Mercy	426570A	11.9	16600	84.0	134000	2.16	143.00	4.10	10.70	99.0	1.3	1.2	5.2	2.10	171	45	173	1	4	
86	Rajendran	750308F	12.3	11900	87.0	12000	2.07	118.00	4.70	14.00	99.0	2.3	2.0	5.0	2.10	225	59	211	1	1	
87	Janakiam...	751174F	9.9	19300	84.0	91000	1.23	139.00	3.40	20.00	99.0	.8	.4	6.4	2.80	66	23	285	1	0	
88	Devi	779868F	12.8	14600	82.0	110000	1.22	134.00	3.80	17.00	99.0	.4	.3	6.2	2.50	110	51	215	1	3	
89	Mohana	751493F	12.1	8200	62.0	79000	1.15	138.00	3.50	20.00	99.0	1.0	.8	5.5	2.50	54	36	130	1	4	

kecaai recently used dialogs

1 : ANApattern																				Visible: 48 of 48 Variabl
	Name	Hospitalno	ANApattern	SOFARespd1	SOFARespd2	SOFARespd3	SOFAPlate...	SOFAPlate...	SOFAPlate...	SOFAVaso...	SOFAVaso...	SOFAVaso...	SOFAGCSd1	SOFAGCSd2	SOFAGCSd3	SOFABild1	SOFABild2	SOFABild3	SOFARena...	SOFARena...
1	ulasi	604475F		0	0	0	3	3	2	0	0	0	0	0	0	0	0	0	2	2
2	nmathi	604723F	3	2	99	99	2	99	99	2	99	99	1	99	99	1	99	99	1	99
3	ajahan	623484F	3	4	1	3	2	3	4	3	0	3	3	3	3	3	2	4	4	
4	anti	611403F		1	1	1	3	2	3	4	1	0	0	0	0	0	0	1	0	
5	nkatesan	611930F	3	1	2	2	3	2	2	0	2	0	1	1	1	2	3	2	2	
6	saratan	618746F	3	1	0	0	1	2	0	0	0	0	0	0	0	0	0	1	0	
7	lhabooba	623442F	3	0	0	99	2	1	99	0	0	99	0	0	99	2	2	99	0	
8	mpath	618921F	3	0	0	0	2	2	1	0	0	0	0	0	0	2	1	0	0	
9	nchana	630681F		1	1	0	4	3	2	4	3	0	3	3	1	2	2	2	0	
10	injula	623849F	3	3	0	0	2	2	0	0	0	0	0	0	0	3	3	1	0	
11	shamma	630468F		0	0	0	4	0	0	0	0	0	0	0	0	0	0	1	0	
12	ralana...	539524F	3	1	0	0	3	3	1	0	0	0	0	0	0	2	2	0	0	
13	mani	001642		0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	
14	hammal	999978d		2	2	1	3	3	3	0	0	0	1	0	0	2	0	0	1	
15	ala	639512F		0	0	99	2	0	99	0	0	99	0	0	99	1	0	99	0	
16	jeshwari	955389C		0	0	99	0	0	99	0	0	99	0	0	99	0	0	99	1	
17	santha...	507937F		1	0	99	4	4	99	0	0	99	0	0	99	0	0	99	0	
18	ayan	647312F		2	2	0	3	3	2	0	0	0	0	0	0	3	3	3	2	
19	shamma	646474F	3	0	0	0	2	2	1	0	0	0	0	0	0	2	1	0	0	
20	dmavathi	297414d		0	0	0	2	0	0	0	0	0	0	0	0	2	1	1	0	
21	nu	639491f	3	0	0	99	2	1	99	0	0	99	0	0	99	0	0	99	0	
22	mala	646573F		0	0	0	0	0	0	3	2	0	0	0	0	0	0	0	1	
23	larmathi	651736f	3	0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	
24	mesh	651630f		0	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	
25	saratha...	651545F		0	0	0	4	3	2	0	0	0	0	0	0	2	2	2	1	

1 : ANApattern																				Visible: 48 of 48 Variabl
	Name	Hospitalno	ANApattern	SOFARespd1	SOFARespd2	SOFARespd3	SOFAPlate...	SOFAPlate...	SOFAPlate...	SOFAVaso...	SOFAVaso...	SOFAVaso...	SOFAGCSd1	SOFAGCSd2	SOFAGCSd3	SOFABild1	SOFABild2	SOFABild3	SOFARena...	SOFARena...
26	ekaraman	651590F		0	0	0	3	3	3	0	0	0	0	0	0	0	0	0	1	0
27	ni	651738F		0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0
28	aranjini	651865F	3	3	1	0	2	3	3	2	0	0	0	0	0	0	0	0	0	0
29	vamma	651766F		3	1	0	2	2	2	3	1	0	0	0	0	2	0	0	2	3
30	imeela...	651827F	3	3	2	0	4	4	4	0	0	0	0	0	0	0	0	0	1	0
31	ra Banu	657019F		2	1	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0
32	ralakshmi	639799F	3	2	0	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0
33	Farahad	646977F		0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
34	ndagao...	657884F		0	0	99	2	2	99	0	0	99	0	0	99	0	0	99	0	0
35	pinath	639794F		0	0	99	4	1	99	0	0	99	0	0	99	0	0	99	0	0
36	ghunad...	639795F		0	0	99	1	1	99	0	0	99	0	0	99	0	0	99	0	0
37	ithu	657779F	3	0	0	0	4	4	2	0	0	0	0	0	0	1	1	1	1	1
38	irugan	955062C		0	0	0	2	2	2	0	0	0	0	0	0	0	0	0	0	0
39	nitha	522157D		2	1	0	2	2	2	3	1	0	0	0	0	0	0	0	2	0
40	canadh...	657895F		0	0	99	1	1	99	0	0	99	0	0	99	0	0	99	1	0
41	esh Ku...	657814F	3	2	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0
42	siammal	338591F	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
43	aylaksh...	650322F	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
44	gadu Raja	657799F	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
45	lbakaran	657890F		0	0	0	2	1	1	0	0	0	0	0	0	3	2	2	0	0
46	la Krish...	657769F		0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	1	0
47	njamal	639822F	3	3	2	1	2	1	0	0	0	0	0	0	0	0	0	0	1	2
48	aram R...	657675F	3	0	0	99	4	0	99	0	0	99	0	0	99	0	0	99	0	0
49	lbavathi	657650F		0	0	99	3	3	99	0	0	99	0	0	99	0	0	99	0	0
50	shnaveni	639846F		2	0	0	0	0	0	2	0	0	0	0	0	0	0	0	2	0

1 : ANApattern																			Visible: 48 of 48 Variab	
	Name	Hospitalno	ANApattern	SOFARespd1	SOFARespd2	SOFARespd3	SOFAPlate...	SOFAPlate...	SOFAPlate...	SOFAVaso...	SOFAVaso...	SOFAVaso...	SOFAGCSd1	SOFAGCSd2	SOFAGCSd3	SOFABilid1	SOFABilid2	SOFABilid3	SOFARena...	SOFARen:
51	Mandotiri	657690F		3	1	2	3	2	1	3	0	0	0	0	0	0	0	0	0	0
52	Govindam...	651978F	3	0	0	99	2	2	99	0	0	99	0	0	99	0	0	99	0	0
53	Gangaiah	651933F		0	0	99	2	2	99	0	0	99	0	0	99	0	0	99	0	0
54	Valarmathy	095895B		0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
55	Kuppuswa...	639809F	3	0	0	0	0	0	0	1	0	0	3	1	0	0	0	0	0	2
56	Bhaskar R...	664501F	3	1	2	0	0	1	1	0	0	0	1	1	0	2	2	2	3	3
57	Venkatala...	657912F	3	4	1	2	4	4	1	3	1	1	0	0	0	2	2	1	1	1
58	Sudhakar	670456F	3	0	0	0	2	3	2	0	0	0	0	0	0	1	1	0	0	0
59	Bujamma	491258C		3	3	1	3	3	2	0	0	0	0	0	0	2	2	2	0	0
60	Mykal	657997F	3	2	2	1	1	0	0	0	0	0	3	3	0	2	1	1	0	0
61	Chandra	664607F	3	0	0	0	4	2	0	0	0	0	0	0	0	3	1	1	0	0
62	Munikann...	671514F	3	2	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
63	Amalmary	671601F	3	2	1	0	3	2	2	0	0	0	0	0	0	0	0	0	1	0
64	Sivasanmu...	664791F	3	1	0	0	2	2	2	0	0	0	0	0	0	0	0	0	1	0
65	Kamalesan	671481F	3	0	0	0	3	4	3	0	0	0	0	0	0	2	2	2	0	0
66	Murugaiyan	671712F		2	0	0	4	2	0	0	0	0	0	0	0	3	3	2	2	2
67	Jayanti	671888F	3	2	1	0	2	1	1	0	0	0	0	0	0	3	3	2	0	0
68	Singanam...	671589F	3	4	3	1	2	3	1	3	0	0	0	0	0	2	2	2	1	1
69	Renammal	675874F		2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0
70	Poomani	329399D		4	4	3	1	1	2	1	1	1	0	0	0	1	1	2	0	0
71	Perumal	691285F	3	3	3	2	2	3	2	1	0	0	0	0	0	1	2	2	1	1
72	Chandra	675699F	5	0	0	99	4	0	99	0	0	99	0	0	99	0	0	99	0	0
73	Rangesh	675573F	5	0	0	99	0	0	99	0	0	99	0	0	99	1	1	99	0	0
74	Samuel	675579F		2	1	0	2	2	2	0	0	0	0	0	0	3	3	3	0	0
75	Jared	675477F	3	0	0	0	3	2	2	0	0	0	0	0	0	1	0	0	0	1

1 : ANApattern																			Visible: 48 of 48 Variab	
	Name	Hospitalno	ANApattern	SOFARespd1	SOFARespd2	SOFARespd3	SOFAPlate...	SOFAPlate...	SOFAPlate...	SOFAVaso...	SOFAVaso...	SOFAVaso...	SOFAGCSd1	SOFAGCSd2	SOFAGCSd3	SOFABilid1	SOFABilid2	SOFABilid3	SOFARena...	SOFARen:
76	Thenmozhi	675321F	3	2	1	0	2	3	2	0	0	0	0	0	0	0	0	0	0	1
77	Andal	675316F	3	1	0	0	1	1	1	3	1	0	0	0	0	0	0	0	0	1
78	Govindasa...	675274F	3	2	0	0	2	2	2	0	0	0	1	0	0	3	3	2	3	3
79	Dhanalaks...	675641F	3	3	1	0	3	3	2	1	1	0	0	0	0	0	0	0	1	1
80	Saraswathi	264141B	3	1	0	0	4	1	1	0	0	0	0	0	0	0	0	0	0	0
81	Panchalai	675876F		0	0	99	2	2	99	0	0	99	0	0	99	3	3	99	1	1
82	Janaki	675667F	3	2	2	0	3	3	3	0	0	0	0	0	0	0	0	0	0	0
83	Kaniyammal	675877F	3	2	1	0	2	2	2	3	0	0	1	0	0	2	1	1	1	1
84	Indirakanti	675875F	3	1	1	0	4	2	2	0	0	0	0	0	0	2	2	2	2	2
85	Mercy	426570A		3	4	4	1	2	2	3	2	2	0	0	0	1	1	1	2	2
86	Rajendran	750308F	3	3	2	2	4	3	3	0	0	0	0	0	0	2	2	0	2	2
87	Janakiam...	751174F		3	3	3	2	3	2	0	0	0	0	0	0	0	0	0	1	0
88	Devi	779868F	5	1	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0
89	Mohana	751493F		4	2	2	2	1	1	4	3	1	0	0	0	0	1	1	0	0

Name		Thulasi																	Visible: 31 of 31 Variab		
	Name	Hospitalno	SOFARena...	SOFARena...	TSOFAd1	TSOFAd2	TSOFAd3	ARDS	Shock	Myocarditis	Renalfailure	AsepMeningitis	PulmEmbolicm	Vasocativegent	Ventilation	NIV	InvasiveVentilat	ICUstay	Hospitalstay	Hospitalome	
1	Thulasi	604475F	2	1	5	5	3	0	0	0	1	0	0	0	0	0	0	3.0	6.0	2	
2	Vanmathi	604723F	99	99	8	99	99	1	1	1	1	0	0	1.0	1.0	0	1.0	0	1.0	1	
3	shajahan	623484F	4	4	20	16	15	1	0	1	0	0	0	1.0	1.0	0	10.0	9.0	10.0	1	
4	Shanti	611403F	0	0	9	4	4	1	0	1	0	0	0	1.0	1.0	1.0	9.0	12.0	15.0	2	
5	Venkatesan	611930F	2	2	9	12	9	1	1	1	0	0	0	1.0	1.0	0	10.0	12.0	20.0	2	
6	Dasaratan	618746F	0	0	3	2	0	1	0	0	0	0	0	0	0	0	0	0	0	8.0	2
7	Mahabooba	623442F	0	99	4	4	99	0	0	0	0	0	0	0	0	0	0	0	0	4.0	2
8	Sampath	618921F	0	0	4	3	1	0	0	0	0	0	0	0	0	0	0	0	0	4.0	2
9	Kanchana	630681F	0	0	14	12	5	0	1	0	0	0	0	1.0	1.0	0	3.0	6.0	12.0	2	
10	Manjula	623849F	0	0	8	5	1	1	0	0	0	0	0	0	0	0	0	3.0	8.0	2	
11	Krishnamma	630468F	0	0	5	0	0	1	0	0	0	0	0	0	0	0	0	0	7.0	2	
12	Guralanar...	539524F	0	0	6	5	1	1	0	0	0	0	0	0	0	0	0	0	6.0	2	
13	Ramani	001642	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	6.0	2	
14	Achammal	999978d	0	0	9	5	4	1	0	0	0	0	0	0	1.0	0	5.0	7.0	11.0	2	
15	Sarala	639512F	0	99	3	0	99	0	0	0	0	0	0	0	0	0	0	0	4.0	2	
16	Rajeshwari	955389C	1	99	1	1	99	0	0	1	0	0	0	0	0	0	0	0	4.0	2	
17	Vasantha...	507937f	0	99	5	4	99	1	0	0	0	0	0	0	0	0	0	0	5.0	2	
18	Vijayan	647312F	2	2	10	10	7	1	0	0	1	0	0	0	0	0	0	0	7.0	2	
19	Pushpamma	646474F	0	0	4	3	1	1	0	0	0	0	0	0	0	0	0	0	6.0	2	
20	Padmavathi	297414d	0	0	4	1	1	0	0	0	0	0	0	0	0	0	0	0	6.0	2	
21	Venu	639491f	0	99	2	1	99	1	0	0	0	0	0	0	0	0	0	0	5.0	2	
22	Nirmala	646573F	0	0	4	2	0	0	1	0	1	0	0	1.0	0	0	0	1.0	6.0	2	
23	Valarmathi	651736f	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	6.0	2	
24	Ramesh	651630f	0	0	1	1	1	0	0	0	0	0	0	0	0	0	0	0	6.0	2	
25	Dasaratha...	651545F	0	0	7	5	4	1	0	0	0	0	0	0	0	0	0	0	7.0	2	

Name		Thulasi																	Visible: 31 of 31 Variab	
	Name	Hospitalno	SOFARena...	SOFARena...	TSOFAd1	TSOFAd2	TSOFAd3	ARDS	Shock	Myocarditis	Renalfailure	AsepMeningitis	PulmEmbolicm	Vasocativegent	Ventilation	NIV	InvasiveVentilat	ICUstay	Hospitalstay	Hospitalome
26	Teekaraman	651590F	0	0	4	3	3	0	0	1	0	0	0	0	0	0	0	0	5.0	2
27	Mani	651738F	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	3.0	2
28	Sivaranjini	651865F	0	0	7	4	3	1	1	1	0	0	0	1.0	1.0	2.0	0	3.0	6.0	2
29	Devamma	651766F	3	1	12	7	3	1	1	0	1	1	0	1.0	1.0	0	7.0	9.0	12.0	2
30	Prameela...	651827F	0	0	8	6	4	1	0	0	1	0	0	0	1.0	3.0	0	3.0	9.0	2
31	Saira Banu	657019F	0	0	3	2	0	1	0	0	0	0	0	0	1.0	2.0	0	2.0	5.0	2
32	Varalakshmi	639799F	0	0	5	0	0	1	0	0	0	0	0	0	0	0	0	0	6.0	2
33	Sk Farahad	646977F	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	7.0	2
34	Kundagao...	657884F	0	99	2	2	99	0	0	0	0	0	0	0	0	0	0	0	3.0	2
35	Gopinath	639794F	0	99	4	1	99	0	0	0	0	0	0	0	0	0	0	0	3.0	2
36	Raghunad...	639795F	0	99	1	1	99	0	0	0	0	0	0	0	0	0	0	0	4.0	2
37	Murthu	657779F	1	1	6	6	4	0	0	0	0	0	0	0	0	0	0	0	6.0	2
38	Murugan	955062C	0	0	2	2	0	0	0	0	0	0	0	0	0	0	0	0	7.0	2
39	Punitha	522157D	0	0	9	4	2	1	1	0	0	0	0	1.0	1.0	0	4.0	7.0	11.0	2
40	Lokanadh...	657895F	0	99	2	1	99	0	0	0	1	0	0	0	0	0	0	0	3.0	2
41	Suresh Ku...	657814F	0	0	4	0	0	1	0	0	0	1	0	0	0	0	0	0	11.0	2
42	Kasiammal	338591F	1	2	0	1	2	0	0	1	0	0	0	0	0	0	0	0	8.0	2
43	Vijaylaksh...	650322F	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7.0	2
44	Jalgaadu Raja	657799F	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	5.0	2
45	Prabakaran	657890F	0	0	5	3	3	0	0	0	0	0	0	0	0	0	0	0	5.0	2
46	Bala Krish...	657769F	0	0	2	1	0	0	0	0	1	0	0	0	0	0	0	0	7.0	2
47	Panjammal	639822F	2	0	6	5	1	1	0	0	0	0	0	0	1.0	0	4.0	5.0	9.0	2
48	Jayaram R...	657675F	0	99	4	0	99	0	0	0	0	0	0	0	0	0	0	0	3.0	2
49	Prabavathi	657650F	0	99	3	3	99	0	0	0	0	0	0	0	0	0	0	0	3.0	2
50	Krishnaveni	639846F	0	0	6	0	0	1	1	0	1	0	0	1.0	0	0	0	3.0	11.0	2

: Name		Thulasi																		Visible: 31 of 31 Varia	
	Name	Hospitalno	SOFARena...	SOFARena...	TSOFAd1	TSOFAd2	TSOFAd3	ARDS	Shock	Myocarditis	Renalfailure	AsepMeningitis	PulmEmbolic	Vasocativegent	Ventilation	NIV	InvasiveVentilat	ICUstay	Hospitalstay	Hospitalome	
51	Mandotiri	657690F	0	0	9	3	3	1	1	0	0	0	0	1.0	1.0	.0	5.0	7.0	9.0	2	
52	Govindam...	651978F	0	99	2	2	99	0	0	0	0	0	0	.0	.0	.0	.0	.0	4.0	2	
53	Gangaiyah	651933F	0	99	2	2	99	0	0	0	0	0	0	.0	.0	.0	.0	.0	4.0	2	
54	Valarmathy	095895B	0	0	0	1	1	0	0	0	0	0	0	.0	.0	.0	.0	.0	6.0	2	
55	Kuppuswa...	639809F	1	0	6	2	0	0	1	0	1	1	0	1.0	.0	.0	.0	3.0	7.0	2	
56	Bhaskar R...	664501F	4	4	7	10	7	1	0	1	1	1	0	.0	.0	.0	.0	3.0	9.0	2	
57	Venkatala...	657912F	0	0	14	8	5	1	1	0	0	0	0	1.0	1.0	.0	.	.	10.0	2	
58	Sudhakar	670456F	0	0	3	4	2	1	0	0	0	1	0	.0	.0	.0	.0	.0	8.0	2	
59	Bujamma	491258C	0	0	8	8	5	1	1	0	0	0	0	.0	1.0	4.0	.0	4.0	8.0	2	
60	Mykal	657997F	0	0	8	6	2	0	0	0	0	1	0	.0	1.0	.0	4.0	4.0	8.0	2	
61	Chandra	664607F	0	0	7	3	1	0	0	0	0	1	0	.0	.0	.0	.0	.0	6.0	2	
62	Munikann...	671514F	0	0	3	0	0	1	0	0	0	0	0	.0	.0	.0	.0	.0	3.0	2	
63	Amalmary	671601F	0	0	6	3	2	1	0	0	1	0	0	.0	1.0	1.0	.0	.0	6.0	2	
64	Sivasanmu...	664791F	1	0	4	3	2	1	1	0	1	0	0	.0	.0	.0	.0	.0	4.0	2	
65	Kamalesan	671481F	0	0	5	6	5	0	0	0	0	0	0	.0	.0	.0	.0	.0	6.0	2	
66	Murugaiyan	671712F	3	2	11	8	4	1	0	0	1	0	0	.0	.0	.0	.0	.0	7.0	2	
67	Jayanti	671888F	0	0	7	5	3	1	0	0	0	0	0	.0	1.0	1.0	.0	.0	8.0	2	
68	Singanam...	671589F	0	0	12	8	4	1	1	1	0	0	0	1.0	1.0	3.0	.0	5.0	10.0	2	
69	Renammal	675874F	0	0	4	1	0	1	0	0	0	0	0	.0	.0	.0	.0	.0	5.0	2	
70	Poomani	329399D	0	0	8	7	8	1	1	0	0	0	0	1.0	1.0	2.0	20.0	24.0	36.0	2	
71	Perumal	691285F	3	2	8	11	8	1	1	0	1	0	0	1.0	1.0	1.0	5.0	10.0	11.0	2	
72	Chandra	675699F	0	99	4	0	99	0	0	0	0	0	0	.0	.0	.0	.0	.0	3.0	2	
73	Rangesh	675573F	0	99	1	1	99	0	0	0	0	0	0	.0	.0	.0	.0	.0	4.0	2	
74	Samuel	675579F	0	0	7	6	5	1	0	0	0	0	0	.0	.0	.0	.0	.0	7.0	2	
75	Jared	675477F	0	0	5	2	2	0	0	0	1	0	0	.0	.0	.0	.0	.0	10.0	2	

: Name		Thulasi																		Visible: 31 of 31 Varia	
	Name	Hospitalno	SOFARena...	SOFARena...	TSOFAd1	TSOFAd2	TSOFAd3	ARDS	Shock	Myocarditis	Renalfailure	AsepMeningitis	PulmEmbolic	Vasocativegent	Ventilation	NIV	InvasiveVentilat	ICUstay	Hospitalstay	Hospitalome	
76	Thenmozhi	675321F	1	1	5	5	3	1	1	0	0	0	0	.0	.0	.0	.0	.0	6.0	2	
77	Andal	675316F	0	0	6	2	1	1	1	0	1	0	0	1.0	.0	.0	.0	.0	5.0	2	
78	Govindasa...	675274F	3	2	11	8	6	1	0	0	0	1	0	.0	.0	.0	.0	.0	7.0	2	
79	Dhanalaks...	675641F	0	0	8	5	2	1	1	0	1	0	0	.0	.0	.0	.0	.0	7.0	2	
80	Saraswathi	264141B	0	0	5	1	1	1	0	0	0	0	0	.0	.0	.0	.0	.0	7.0	2	
81	Panchalai	675876F	0	99	6	5	99	0	0	0	0	0	0	.0	.0	.0	.0	.0	4.0	2	
82	Janaki	675667F	0	0	5	5	3	1	0	0	0	0	0	.0	.0	.0	.0	.0	5.0	2	
83	Kaniyammal	675877F	0	0	11	4	3	1	1	0	1	0	0	1.0	1.0	2.0	.0	3.0	7.0	2	
84	Indirakanti	675875F	2	2	9	7	6	1	1	0	1	0	0	.0	.0	.0	.0	.0	6.0	2	
85	Mercy	426570A	0	0	10	9	9	1	1	1	1	0	0	1.0	1.0	1.0	13.0	14.0	14.0	1	
86	Rajendran	750308F	1	0	11	8	5	1	0	0	1	0	0	.0	1.0	.0	5.0	6.0	8.0	2	
87	Janakiam...	751174F	2	3	6	8	8	1	0	0	1	0	0	.0	1.0	2.0	10.0	13.0	24.0	2	
88	Devi	779868F	0	0	2	1	1	1	0	0	0	0	0	.0	.0	.0	.0	.0	5.0	2	
89	Mohana	751493F	1	0	10	8	5	1	1	1	1	0	0	1.0	1.0	1.0	6.0	7.0	9.0	2	



I : Name		Thulasi											
	Name	HospitalNo	ProbableC...	Billclass	Bill	APACHE1a	APACHE1b	APACHE1c	APACHEto...	ANArpt	ANArptpatte rn	ANArepeatvalue	ANAPositive
1	Thulasi	604475F		2	40286	76	0	5	81	.	.	.	0
2	Vanmathi	604723F	ards	2	11521	76	0	12	88	.	.	.	1
3	shajahan	623484F	arf/ards	4	125891	115	13	12	140	.	.	.	1
4	Shanti	611403F		4	160188	42	0	5	47	.	.	.	0
5	Venkatesan	611930F		4	111678	80	0	9	89	.	.	.	1
6	Dasaratan	618746F		3	53896	22	0	5	27	.	.	.	1
7	Mahabooba	623442F		2	11060	23	0	0	23	.	.	.	1
8	Sampath	618921F		2	10531	36	0	0	36	5	5	0	1
9	Kanchana	630681F		3	87337	34	13	3	50	.	.	.	0
10	Manjula	623849F		2	36313	38	0	9	47	0	.	0	1
11	Krishnamma	630468F		2	38779	30	0	0	30	.	.	.	0
12	Guralanar...	539524F		2	17651	41	0	5	46	.	.	.	1
13	Ramani	001642		2	11270	24	0	0	24	.	.	.	0
14	Achammal	999978d		4	121816	54	0	5	59	.	.	.	0
15	Sarala	639512F		2	10567	33	0	0	33	.	.	.	0
16	Rajeshwari	955389C		1	5781	21	0	0	21	.	.	.	0
17	Vasantha...	507937f		1	8793	34	0	3	37	.	.	.	0
18	Vijayan	647312F		2	20286	25	0	5	30	.	.	.	0
19	Pushpamma	646474F		2	17317	12	0	0	12	.	.	.	1
20	Padmavathi	297414d		2	13781	27	0	0	27	.	.	.	0
21	Venu	639491f		2	15821	36	0	0	36	.	.	.	1
22	Nirmala	646573F		2	41156	36	0	5	41	.	.	.	0
23	Valarmathi	651736f		2	15244	19	0	0	19	.	.	.	1
24	Ramesh	651630f		1	9504	13	0	0	13	.	.	.	0
25	Dasaratha...	651545F		2	25548	33	0	0	33	.	.	.	0

I : Name		Thulasi											
	Name	HospitalNo	ProbableC...	Billclass	Bill	APACHE1a	APACHE1b	APACHE1c	APACHEto...	ANArpt	ANArptpatte rn	ANArepeatvalue	ANAPositive
26	Teekaraman	651590F		2	13654	32	0	5	37	.	.	.	0
27	Mani	651738F		1	6801	13	0	0	13	.	.	.	0
28	Sivaranjini	651865F		2	48688	32	0	5	37	5	5	0	1
29	Devamma	651766F		4	146441	42	0	0	42	.	.	.	0
30	Prameela...	651827F		2	37778	47	0	2	49	1	3	1	1
31	Saira Banu	657019F		2	41191	38	0	5	43	.	.	.	0
32	Varalakshmi	639799F		2	22786	20	0	5	25	0	.	0	1
33	Sk Farahad	646977F		2	29045	32	0	5	37	5	.	0	0
34	Kundagao...	657884F		1	7250	14	0	0	14	.	.	.	0
35	Gopinath	639794F		1	6087	14	0	3	17	.	.	.	0
36	Raghunad...	639795F		1	9782	32	0	0	32	.	.	.	0
37	Muthu	657779F		2	10085	20	0	0	20	0	.	0	1
38	Murugan	955062C		2	25248	28	0	5	33	.	.	.	0
39	Punitha	522157D		3	85787	69	5	9	83	.	.	.	0
40	Lokanadh...	657895F		1	6421	18	0	0	18	.	.	.	0
41	Suresh Ku...	657814F		3	71240	39	0	0	39	0	.	0	1
42	Kasiammal	338591F		2	34658	21	0	0	21	1	3	1	1
43	Vijaylaksh...	650322F		2	21473	10	0	5	15	5	5	0	1
44	Jalgadu Raja	657799F		2	13799	12	0	0	12	.	.	.	1
45	Prabakaran	657890F		2	10159	32	0	0	32	.	.	.	0
46	Bala Krish...	657769f		2	18587	28	0	0	28	.	.	.	0
47	Panjammal	639822F		4	124711	78	0	5	83	2	3	1	1
48	Jayaram R...	657675F		1	7448	7	0	0	7	0	.	0	1
49	Prabavathi	657650F		1	7130	27	0	0	27	.	.	.	0
50	Krishnaveni	639846F		4	109317	37	0	9	46	.	.	.	0

1 : Name		Thulasi											
	Name	HospitalNo	ProbableC...	Billclass	Bill	APACHE1a	APACHE1b	APACHE1c	APACHEto...	ANArpt	ANArptpatte rn	ANArepeatvalue	ANAPositive
51	Mandotiri	657690F		3	56601	34	0	0	34	.	.	.	0
52	Govindam...	651978F		2	10462	28	0	0	28	0	.	0	1
53	Gangaiah	651933F		1	8405	5	0	0	5	.	.	.	0
54	Valarmathy	095895B		2	12154	30	0	0	30	.	.	.	0
55	Kuppuswa...	639809F		2	34498	38	0	0	38	.	.	.	1
56	Bhaskar R...	664501F		3	53248	69	0	9	78	.	.	.	1
57	Venkatala...	657912F		4	110598	112	0	0	112	0	.	0	1
58	Sudhakar	670456F		2	26285	27	0	0	27	.	.	.	1
59	Bujamma	491258C		2	44162	60	0	5	65	.	.	.	0
60	Mykal	657997F		4	105330	24	13	0	37	.	.	.	1
61	Chandra	664607F		2	26594	32	0	0	32	0	.	0	1
62	Munikann...	671514F		1	7468	26	0	0	26	.	.	.	1
63	Amalamary	671601F		2	24560	62	0	5	67	5	5	0	1
64	Sivasanmu...	664791F		2	14287	46	0	5	51	5	5	0	1
65	Kamalesan	671481F		2	10395	28	0	0	28	0	.	0	1
66	Murugaiyan	671712F		2	23159	58	0	0	58	.	.	.	0
67	Jayanti	671888F		2	27765	33	0	0	33	0	.	0	1
68	Singanam...	671589F		3	84996	65	0	0	65	.	.	.	1
69	Renammal	675874F		1	9996	59	0	2	61	.	.	.	0
70	Poomani	329399D		4	286354	35	0	1	36	.	.	.	0
71	Perumal	691285F		4	164894	78	0	9	87	0	.	0	1
72	Chandra	675699F		1	4482	17	0	0	17	0	.	0	1
73	Rangesh	675573F		1	8579	17	0	0	17	5	5	0	1
74	Samuel	675579F		2	18217	30	0	5	35	.	.	.	0
75	Jared	675477F		2	38936	46	0	3	49	.	.	.	1

76 : Name		Thenmozhi											
	Name	HospitalNo	ProbableC...	Billclass	Bill	APACHE1a	APACHE1b	APACHE1c	APACHEto...	ANArpt	ANArptpatte rn	ANArepeatvalue	ANAPositive
76	Thenmozhi	675321F		2	14682	33	0	5	38	0	.	0	1
77	Andal	675316F		2	16364	44	0	5	49	4	3	1	1
78	Govindasa...	675274F		2	18509	59	3	5	67	5	5	0	1
79	Dhanalaks...	675641F		2	19402	51	0	5	56	0	.	0	1
80	Saraswathi	264141B		2	30185	38	0	5	43	5	5	0	1
81	Panchalai	675876F		1	6247	27	0	0	27	.	.	.	0
82	Janaki	675667F		2	11173	32	0	3	35	0	.	0	1
83	Kaniyammal	675877F		2	48155	68	0	5	73	2	3	1	1
84	Indirakanti	675875F		2	15910	69	0	5	74	0	.	0	1
85	Mercy	426570A	mods	2	322606	68	0	0	68	.	.	.	0
86	Rajendran	750308F		3	85465	85	0	5	90	5	5	0	1
87	Janakiam...	751174F		4	296772	48	0	0	48	.	.	.	0
88	Devi	779868F		2	11512	40	0	5	45	5	5	0	1
89	Mohana	751493F		3	97554	45	0	3	48	.	.	.	0