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Association of Anaemia & Urinary Tract Infections with *Amavata* (Rheumatoid Arthritis) – A matched case-control study carried out at Jamnagar, Gujarat, India

Research Article

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Abstract

Background: *Amavata* (Rheumatoid Arthritis) is a chronic progressive disease, resulted from the conglomeration of *Ama* and aggrevated *Vata dosha* which gets lodged in the small joints followed by large joints. If it is left untreated, may cause various complications in the form of *Vataja* diseases in which *Raktadhatu kshaya* (Anaemia) and *Mutrakricchra* (Urinary Tract Infection) are predominant. But it needs robust evidence to revalidate the same. Aim & Objective: To evaluate the association of *Raktadhatu kshaya* (Anaemia) and *Mutrakricchra* (Urinary Tract Infection) with *Amavata* (~Rheumatoid Arthritis). Materials & Methods: A case-control study was conducted from 18.04.2018 to 09.01.2020, containing 155 cases (patients of *Amavata*), and 163 controls (healthy volunteers), matching in age (between 18 to 50 years), and sex, selected from Jamnagar district. Health Assessment proforma of TRISUTRA project CSIR-AYURGENOMICS for health assessment, ACR, 1987 Criteria for RA diagnosis were used. Chi-square test was applied to find the association of *Raktadhatu kshaya* (Anaemia) and *Mutrakricchra* (Urinary Tract Infection) with *Amavata* whereas Unpaired or Mann-whitney U test was applied to compare the hematological parameters between case and control group. Results: Statistically significant differences were found in the mean values of haemoglobin, total leukocyte count, neutrophils, lymphocytes, eosinophils, monocytes, MCV, MCH, MCHC, PCV, total RBC count, and platelet count among both the groups. Microcytic and Dimorphic Anaemia were substantially higher ($P<0.0001$) in the *Amavata* patients than in the controls (χ^2 value=24.814). The prevalence of UTI (presence of pus cells in the urine) was found significantly more ($P<0.0001$) in *Amavata* patients than healthy individuals (χ^2 value=45.347). Conclusion: Anaemia and Urinary tract infections are strongly associated with *Amavata* (~Rheumatoid Arthritis).

Key Words: *Amavata,* Anaemia, Case-control study, Haematological parameters, Rheumatoid Arthritis, Urinary Tract Infection.

Introduction

The word '*Amavata'* is a conglomeration of '*Ama'* and '*Vata'*. *Madhava Nidana*, a medieval treatise of ayurvedic diagnostic system and pathology, is the first one to propose the disease *Amavata* to the ayurvedic fraternity. *Amavata* can be correlated with Rheumatoid Arthritis (RA) in contemporary medicine, its etiology includes excessive intake of *Guru* (heavy), *Snigdha* (oily), *Viruddhahara* (incompatible), *Asatmya* and *Apathya* (unwholesome), and irregular diet intake, which impairs *Agni* (a digestive mechanism), results in *Agnimandya* (indigestion), the primary step in the formation of *Ama* (undigested material) (1). If this *Ama* combines with vitiated *Vata dosha* and while circulating all over the body, it gets lodged in joints and results in *Sandhi-Shoola* (joint pain), *Sandhi-Shotha* (swelling in the joints), *Jwara* (fever), *Sandhi-Stabdhata* (stiffness in joints), loss of appetite, indigestion, and body ache (2). The potential complications of *Amavata* include *Jadata* (ankylosis of the joint), *Sankocha* (abnormally fixed state of any limb in flexion or inability to extend the limb), *Khanjata* (affliction of *Kandara* in the thigh region), *Angavaikalya* (swan-neck buttonhole deformity, z-deformity, ulnar deviation, cock-up toe deformity etc.) *Granthi* (subcutaneous nodules), and other *Vataja* disorders. These complications have arisen from the *Amayuktarasadhatu* which cannot continue *Uttarottara Dhatuposhana*, thereby it worsens the quality of life of the patient. The disturbed *Dhatuposhana* (sequential nourishment of body tissues) may lead to *Ojokshaya* also, which may stimulate the pathogenesis of other diseases. *Raktadhatu kshaya* (anaemia) and *Mutrakricchra* (urinary tract infection) also come under *Vataja* diseases as *anya Upadrava* (complications).

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Rheumatoid Arthritis is an auto-immune, chronic, progressive, and degenerative disorder with unconfirmed etiology. This non-communicable condition affects roughly 0.5 percent to 1 percent of individuals worldwide (3, 4). It affects more females than males, particularly the middle-aged. Joint degradation, significant disability, diminished quality of life, the introduction of comorbidities, and early death may all occur if RA is not treated or managed at the appropriate time (5). Cardiovascular disease (CVD), cancer (particularly lymphoma and lymphoproliferative disorders, lung cancer, and melanoma), infections, depression, and gastrointestinal sickness are all possible comorbidities (6, 7). However, the prognosis is so bad that there is a possibility of making life difficult by joint deformity and continuous pain. The pathogenesis not only affects joints but also involves the heart too. So that patients experience heaviness in the heart and asthma, some patients develop anaemia too. These literature-based statements are to be validated by strong evidence.

As per the *Karana-Karya Siddhanta* (theory of cause and effect), the knowledge of effect or outcome can be ascertained by the knowledge of exposure or cause. '*Sheshavat Anumana',* way of reasoning in Ayurveda is a classic example of shreds of evidence gained via retrospective research in Ayurveda (8). Finding a current result of interest and investigating its historical source is one strategy to generate evidence-based retrospective studies (9). Before initiating or administering or introducing any particular intervention or treatment in a specific disease condition, an observational study is required to know the weightage of its incidence, etiological factors, and vulnerability. The direction of a causal link (*Karya-Karana-bandha*) is usually determined by the temporal alignment of the exposure (cause) and the result (effect).

Hence, the present study has focused on Anaemia and Urinary tract infections and to find out their relation with *Amavata* by adopting a retrospective epidemiological analytical study i.e. Case-control study with the following aim & objectives.

Aim

To evaluate the association of *Raktadhatu kshaya* (Anaemia) and *Mutrakricchra* (Urinary Tract Infection) with *Amavata* (~Rheumatoid Arthritis).

Objectives

- To compare the hematological parameters in the patients of *Amavata* and Healthy individuals.
- To assess the complete urine examination in the patients of *Amavata* and Healthy individuals.

Materials & Procedures

A case-control study was conducted. Case-control research aids in establishing the covalent bond between the disease and its etiological factors and also reveals the relative predominance among them. This approach in epidemiology enables the researcher to reach his destiny when the findings are generalized or applied to the population, possible only by the comparison of risk factors observed in the diseased population with healthy individuals. So, the case-control approach in observational studies helps to conclude the susceptible, preventive, and therapeutic measures. It always aims at finding the provoking factor in diseased persons as well as what is the preventive or protecting factor in healthy individuals (10).

Study sample

In the present study, the cases (patients of *Amavata*) and controls (healthy volunteers) were taken as a 1:1 ratio matching with age and sex in both the groups. A total of 155 cases and 163 controls were selected through the convenience sampling method, interviewed, and the history related to the present study was collected through the direct interview method.

Inclusion criteria for cases

Diagnosed patients of *Amavata* who aged above 18 years and under 50 years of either sex (those who were having the symptoms of *Amavata* (11) and fulfilling the ACR, 1987 Criteria (12) with positive RA factor-quantitative and CRP-quantitative) for less than or equal to 5 years were considered as the case group. From 18th April, 2018 to 9th January, 2020, both incidence and prevalent cases attending OPD and IPD of IPGT& RA Hospital, Jamnagar, and those prepared to give written informed consent were recruited in the research.

Inclusion criteria for controls

Controls were healthy individuals without any disease condition, fulfilled the eligibility criteria and who were matched in age and sex with cases, and drawn from the same source of population. Every control was screened initially through a health assessment questionnaire designed by CSIR-Ayurgenomics unit-TRISUTRA project, CSIR-IGIB, New Delhi to confirm them as healthy individuals followed by the investigations mentioned above, those who came under the normal range of RA factor, CRP, and who were prepared to give written informed consent were recruited for the present work.

Exclusion criteria for cases

Amavata patients with other comorbidities such as diabetes, hypothyroidism, or any other endocrinal and metabolic disorders, less than 18 and more than 50 years of age, and those who refused to participate in the study were excluded.

Exclusion criteria for controls

Unhealthy individuals, less than 18 and more than 50 years of age, and those who were not willing to participate in the study were excluded.

Ethical clearance

The Institutional Ethics Committee of the Gujarat Ayurved University's IPGT &RA, Jamnagar, gave their approval; vide **Ref. PGT/7-A/Ethics/2017-18/3042 dated 19/02/2018.**

CTRI Registration

The Clinical Trial Registry-India (CTR-I) has been notified about this trial and registered prospectively vide CTRI/2018/04/013241 [Registered on 13/04/2018].

Processing of sample for Complete Blood Picture (CBP) and Complete Urine Examination (CUE)

The blood samples were drawn from each enrolled participant (both the cases & controls) after providing the prior written informed consent only. Heparinized tubes or vacutainers were used to collect the blood sample, containing ethylenediaminetetraacetic acid disodium salt (EDTA-2Na) and also in a plain tube or without EDTA coated vacutainers. The analysis was done through the Sysmex XP-300 Automated Haematology analyzer. To determine the general blood picture (GBP) of the blood sample was done through the manual method with the help of a microscope. The urine sample was collected in a plain container, sent for microscopic examination through a manual method. The presence of pus cells a minimum of 6 to 10 is considered as infection of the urinary tract (UTI-Urinary Tract Infection). Both the analyses were done in clinical laboratories of IPGT & RA Hospital, Jamnagar, Gujarat, India.

Statistical analysis

The Chi-square test has been applied to test the matching criteria in terms of age and sex (male or female) in both the cases and controls. The same test has been applied to evaluate the association of GBP and UTI with *Amavata*. For the comparison of levels of blood components like Haemoglobin, TLC (Total Leucocyte Count), DC-N (Differential Count – Neutrophils), DC-L (Differential Count–Lymphocytes), DC-E (Differential Count– Eosinophils), DC-M (Differential Count–Monocytes), PCV (Packed Cell Volume), MCV (Mean Corpuscular Volume), MCH (Mean Corpuscular Haemoglobin), MCHC (Mean Corpuscular Haemoglobin Concentration), Platelet count, and RBC (Red Blood Cells) count, Mann-Whitney U test or Unpaired t-test (if the data followed normal distribution) has been applied. SPSS (Statistical Package for Social Sciences) version 20.0 was used to handle all of these statistical measures. Tables- 1, 2, 3, and 4 show the outcomes of these tests.

Table-1: Distribution of Age group and Gender in both the groups (Cases and controls)

Variable	Level code	Label	Cases (N)	Controls (N)	χ^2 value	P-value
Age group	1	18-30	30 (19.35%)	38 (23.31%)	2.354	0.308
	2	31-40	62 (40%)	52 (31.90%)		
	3	41-50	63 (40.67%)	73 (44.79%)		
Gender	1	Male	23 (14.84%)	24 (14.72%)	0.001	0.977
	2	Female	132 (85.16%)	139 (85.28 %)		

Table-2: Comparison of Haematological parameters in case and control groups

Name of the Parameter	Group	Mean ± S.D	P-Value, Inference
Haemoglobin (in gms. %)	Case (n=155)	11.55 ±1.63	< 0.0001, Extremely Significant
	Control (n=163)	12.29±1.47	
Total Count (/Cumm)	Case (n=155)	7501.47±2050.15	< 0.0001, Extremely Significant
	Control (n=163)	6485.20±1529.63	
DLC-Neutrophils (%)	Case (n=155)	64.45±7.85	< 0.0001, Extremely Significant*
	Control (n=163)	59.17±7.38	
DLC-Lymphocytes (%)	Case (n=155)	28.95±7.33	< 0.0001, Extremely Significant
	Control (n=163)	34.84±7.99	
DLC-Eosinophils (%)	Case (n=155)	3.04±2.88	0.0063, Very Significant
	Control (n=163)	3.26±2.05	
DLC-Monocytes (%)	Case (n=155)	3.47±1.29	0.0006, Extremely Significant
	Control (n=163)	3.01± 1.04	
MCV (fL)	Case (n=155)	75.65±9.27	0.0575, Not Significant
	Control (n=163)	77.65±8.19	
MCH (pg)	Case (n=155)	24.84±3.35	0.0026, Very Significant
	Control (n=163)	26.04±3.71	
MCHC (%)	Case (n=155)	32.6±1.66	0.0020, Very Significant
	Control (n=163)	33.1±1.66	
PCV (%)	Case (n=155)	35.16±4.33	0.0007, Extremely Significant
	Control (n=163)	36.86±4.02	
Total RBC Count (Mil. /Cumm)	Case (n=155)	4.58±0.55	0.0042, Very Significant
	Control (n=163)	4.76±0.54	
Platelet Count (/Cumm)	Case (n=155)	3.56±0.95	< 0.0001, Extremely Significant
	Control (n=163)	3.13±0.82	

DLC: Differential Count, MCV: Mean Corpuscular Volume, MCH: Mean Corpuscular Hemoglobin, MCHC: Mean Corpuscular Hemoglobin Concentration, PCV: Packed Cell Volume, RBC: Red Blood Cells count, S.D.: Standard deviation. *-Unpaired t test

Table-3: Distribution of general blood picture among cases and controls

GROUP	General Blood Picture			χ^2 value	P value	Statistical Inference
	Normal	Dimorphic Anaemia	Microcytic Hypochromic Anaemia			
Case (n=155)	96 (61.9%)	11(7.1%)	48 (31%)	24.814	<0.0001	Extremely significant
Control (n=163)	140 (85.9%)	2 (1.2%)	21 (12.9%)			

Table-4: Distribution of Urinary Tract Infection (UTI) among cases and controls

GROUP	UTI		χ^2 value	P value	Statistical Inference
	Absent	Present			
Case (n=155)	101 (65.2%)	54 (34.8%)	45.347	<0.0001	Extremely significant
Control (n=163)	155 (95.1%)	8 (4.9%)			

Figure 1: Barchart depicting the distribution of General blood picture in both the groups

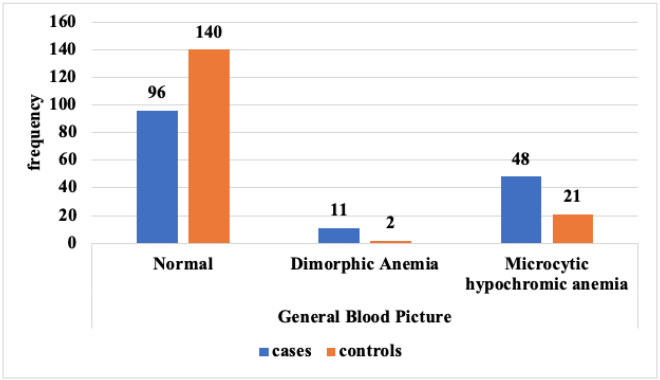
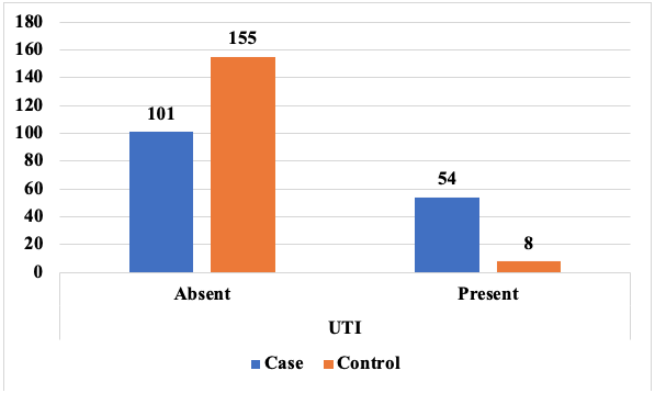


Figure 2: Bar chart depicting the distribution of UTI in both the groups



Observations & Results

In the table-1, age group and gender of both the groups were documented along with their Chi-square values, which were found to have non-significant associations. The mean values of Haemoglobin (in gms. %), Total Count (/Cumm), DLC-Neutrophils (%), DLC-Lymphocytes (%), DLC-Eosinophils (%), DLC-Monocytes (%), MCV (fL), MCH (pg), MCHC (%), PCV (%), Total RBC Count (Mil. /Cumm), and Platelet Count (/Cumm) were documented in the Table-2 along with their U (Mann-Whitney U test) or T (Unpaired t-test) values. All the parameters were found statistically different among both groups. The frequency of GBP (Normal or Dimorphic Anaemia or Microcytic Hypochromic Anaemia) and UTI in both the groups along with its chi-square values are presented in Table-3 and 4 respectively, which were shown significant association.

Discussion

The ratio of cases and controls in the present study was nearly 1:1. The case group (N=155) had an average age of 39.35± 9.115 years. The control group (N=163) had an average age of 38.49±8.937 years. Both the groups were matched by their age and sex. Hence, age and sex were found statistically insignificant. Sex-wise, the majority of the subjects were females (N=132), covering 85.16%, as *Amavata* (Rheumatoid Arthritis) mainly affects the women population.

The mean level of haemoglobin in the case group is 11.55 ± 1.63 gms % (Mean ± S.D.), comparatively less than the mean levels of haemoglobin of the control group i.e., 12.29 ± 1.47gms % (Mean ± S.D.). The mean total RBCs (Red Blood Cells count) of the case group is 4.58 ± 0.55 million/Cumm (Mean ± S.D.), comparatively less than the mean total RBCs of the control group i.e., 4.76 ± 0.54 million/Cumm (Mean ± S.D.). The mean PCV of the case group is 35.16 ± 4.33 % (Mean ± S.D.), comparatively less than the mean PCV of the control group i.e., 36.86 ± 4.02 % (Mean ± S.D.). The mean MCV (Mean Corpuscular Volume) of the case group is 75.65 ± 9.27 fL (Mean ± S.D.), comparatively less than the mean MCV of the control group i.e., 77.65 ± 8.19 fL (Mean ± S.D.). The mean MCH (Mean Corpuscular Haemoglobin) of the case group is 24.84 ± 3.35 Pg (Mean ± S.D.), comparatively less than the mean MCH of the control group i.e., 26.04 ± 3.71 Pg (Mean ± S.D.). The mean MCHC (Mean Corpuscular Haemoglobin Concentration) of the case group is 32.6 ± 1.66 gms % (Mean ± S.D.), comparatively less than the mean MCHC of the control group i.e., 33.1 ± 1.66 gms % (Mean ± S.D.). It indicates the prevalence of anaemia in the case group that is Rheumatoid anaemia. Rheumatoid anaemia is a common type of chronic illness anaemia (ACD). It's not the same as iron deficiency anaemia or iatrogenic anaemia, for example. Rheumatoid anaemia is characterized by normochromic, normocytic, or, less often, microcytic, regenerative, and thrombocytosis. Serum transferrin levels are normal or low, transferrin saturation is decreased, serum ferritin levels are normal or high, the soluble transferrin receptor (stfr) is not

increased (a distinguishing feature with iron deficiency anemia), and the stfr/log ferritin ratio is lower than 1.

Hepcidin, in association with the cytokine interleukin-6, is now recognised as a crucial factor in Rheumatoid Anaemia (IL-6). Hepcidin is a hormone that controls iron transport across membranes, preventing iron from leaving enterocytes, macrophages, and hepatocytes. Hepcidin also limits iron absorption in the intestine and iron release from macrophages and hepatocytes. Hepcidin's effect is mediated by its interaction with the iron exporter ferroprotein. The protein hemojuvelin is required for hepcidin expression in the liver. Hepcidin synthesis is raised by inflammation through IL-6, but it is suppressed by iron shortage and variables associated with enhanced erythropoiesis (hypoxia, haemorrhage, hemolysis, dyserythropoiesis). IL-6 reduces the number of nucleated erythroid cells in the bone marrow and decreases blood iron levels, both of which may be reversed with the use of an IL-6 antagonist. Hepcidin gene transcription is stimulated by IL-6, especially in hepatocytes. Human hepatocytes were exposed to a panel of cytokines, and it was discovered that IL-6, but not TNF or IL-1, stimulated hepcidin mRNA production ([13). Experiments are increasingly suggesting that the hepatocyte is not only the iron storage depot but also the 'command center' for maintaining iron homeostasis. It receives numerous iron balance cues and reacts by controlling hepcidin antimicrobial peptide transcription (14).

The physiology mentioned above influences RBCs' count (Red Blood Cells), Packed Cell Volume (PCV), and other blood indices too such as MCV, MCH, MCHC. The mean Platelet count of the case group is 3.56 ± 0.95 10^3/ul (Mean ± S.D.), comparatively greater than the mean Platelet count of the control group i.e., 3.13 ± 0.82 10^3/ul (Mean ± S.D.). This suggests that thrombocytosis is linked with more severe rheumatoid arthritis and is caused by a compensatory increase in platelet formation caused by active intravascular coagulation (15). Inflammation and coagulation are intimately related, with inflammation tipping the homeostatic balance in favour of thrombosis and increasing cardiovascular morbidity. Indeed, inflammation activates the coagulation system by disrupting the usual physiologic anticoagulant processes, with interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-) as key actors. Platelets emit pro-inflammatory platelets microparticles when activated, which interact with leucocytes and cause rheumatoid arthritis joint and systemic inflammation (16).

The mean of total Leucocyte count in the case group i.e., 7501.47 ± 2050.15/ cumm is slightly greater than the mean value of the control group i.e. 6485 ± 1529.63/cumm. In the same way, total Neutrophil and Monocyte counts in the case group i.e., 64.45 ± 7.85 % & 3.47 ± 1.29 % are slightly greater than the mean value of the control group i.e. 59.17 ± 7.38 % & 3.01 ± 1.04 %. It indicates Neutrophilic leucocytosis. It is because of the primary immune response and endothelial dysfunction, which is also associated with thrombocytosis (17). It might be due to the previous usage of corticosteroid therapy, and most of the subjects in the case group are having a chronic type of disease in the present study. On the other hand, the mean Lymphocytes and Eosinophil counts are comparatively less in the case group than the control group, which indicates the compromised immune system among case group individuals.

Microcytic and Dimorphic Anaemias were found more in the case group than in the control group. Out of 59 anaemic individuals of the case group, 48 patients were found to have microcytic anaemia whereas 11 patients were found to have dimorphic anaemia. It illustrates the inevitability of *Vata Dosha* predominance with its *Ruksha Guna* (dry quality) and is responsible for *Dhatukshaya* in the case group. Moreover, the presence of *Ama* prevents or obstructs the *Uttarottara Dhatuposhana* (malnourishment of body tissue elements in sequential order). The most prevalent extra-articular symptom of Rheumatoid Arthritis is chronic illness anaemia (ACD).

Anaemia is defined as a reduction in the number of circulating red blood cells (RBCs), haemoglobin (Hb), or the volume of packed RBCs (hematocrit) (18). In contemporary research, the inflammation absorbs the Iron and Calcium from Red blood cells (RBCs), which results in anaemia. Inflammation occurs in the joints and other tissues as a result of the immunological response. Inflammation in the bone marrow may reduce the generation of red blood cells. It may cause the release of particular proteins that influence the body's iron use. Inflammation may also alter the body's synthesis of erythropoietin, a hormone that regulates red blood cell production (19). It is also established that the accumulation of osteoblast cells in the bone marrow and production of sideroblasts (nucleated erythroblasts-precursors to mature red blood cells) results in refractory anaemias in RA patients (20).(Figure 1)

The prevalence of UTI (presence of pus cells in the urine) is found to have more in the *Amavata* group i.e., 34.67% when compared with the control group or healthy volunteers (4%). Out of 52 UTI patients of the case group, 43 were had *Vata Pradhana Deha-Prakriti*. It indicates the urinary tract infections are more in *Amavata* patients, particularly in *Vata Pradhana Deha-Prakriti* individuals, because of less *vyadhikshmatva* (immunity) and less *bala* (strength). Urinary tract infections (UTI), upper respiratory tract infections (URTI), skin and soft tissue infections, pneumonia, and joint infections are the most frequent infections recorded in people with established Rheumatoid Arthritis. Increased infection susceptibility in Rheumatoid Arthritis is likely complex, owing to the disease's underlying immunologic abnormalities, the use of immunosuppressive medications, and hereditary predisposition. According to Hughes LB, Criswell LA, Beasley TM, et al., Urinary tract infection (UTI) was associated with the TNF 238 A and LTA þ 365 C alleles, and marginally with the FCGR3A F allele. There was also a strong linear association between UTI and the number of risk alleles specified by these three SNPs, suggesting that these three SNPs had a cumulative influence on susceptibility. These results have

significant implications for the role of genetics in bacterial and viral infection susceptibility (21). (Figure 2)

Conclusion

Based on the above observations, statistical analysis, and discussion; it is concluded that anaemia and urinary tract infections are strongly associated with *Amavata* (~Rheumatoid Arthritis). If the disease progresses, these complications may also increase and worsen the daily routine of the patient and thereby cause other complications, too. Hence, the physician should be cautious while treating the patient of *Amavata* and prescribe *Deepana* (drugs that induce digestive fire), *Pachana* (drugs that fasten the digestion) drugs to prevent the recurrence of *Ama* production, and include *Rakta Vardhaka Ahara* (food substances that increase the blood components) and immuno-modulatory food substances in the diet chart of patient.

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Conflicts of Interest: None

Abbreviations

- CSIR- Council of Scientific and Industrial Research,
- IGIB- Institute of Genomics and Integrative Biology,
- TRISUTRA- Translational Research and Innovative Science Through Ayurveda,
- DLC- Differential Count,
- MCV- Mean Corpuscular Volume,
- MCH- Mean Corpuscular Hemoglobin,
- MCHC- Mean Corpuscular Hemoglobin Concentration,
- PCV- Packed Cell Volume,
- RBC- Red Blood Cells,
- UTI- Urinary Tract Infection,
- IPGT & RA- Institute for Post-Graduate Teaching and Research in Ayurveda.

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