

Age, Urban-Rural, Gender, and Sex-Based Differences in Autoimmune and Autoinflammatory Diseases: A Cross-Sectional Study

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How to cite this paper: Keïta, K., Camara, B.D., Doumbia, A.A., Kamissoko, C.O., Tolo, N., Doumbia, N., Berthé, B.B., Sangaré, D., Saliou, M., Dembélé, I.A., Cissoko, M., Fofana, Y., Sy, D., Traoré, D., Kaya, A.S., Dembélé, M., Keïta, A., Diawara, A., Wélé, M., Traoré, K., Shaffer, J.G., Diakité, M. and

Abstract

Introduction: There are no studies that have explored globally and exhaustively the relationship between age group, urban-rural, gender and sex, and the autoimmune diseases' nosological entity, autoimmune diseases' nosological sub-entities, each of the autoimmune diseases, and autoinflammatory diseases' nos-

Traoré, H.A. (2025) Age, Urban-Rural, Gender, and Sex-Based Differences in Autoimmune and Autoinflammatory Diseases: A Cross-Sectional Study. *Open Journal of Internal Medicine*, **15**, 354-376.

<https://doi.org/10.4236/ojim.2025.154032>

Received: November 11, 2025

Accepted: December 6, 2025

Published: December 9, 2025

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ological entity, autoinflammatory diseases' nosological sub-entities, each of the autoinflammatory diseases. **Methods:** To determine globally and exhaustively the age, urban-rural, gender, and sex-based differences in autoimmune diseases and autoinflammatory diseases, a 15-year cross-sectional study was conducted in the Department of Internal Medicine at the University Hospital Center of the Point G. A bivariate analysis using the Chi-square and Fisher's exact tests to assess the statistical significance and strength of the associations between the categorical independent variables and the outcome variables was performed. A two-tailed p-value < 0.05 was retained and considered statistically significant. **Results:** The age group of 20 - 39 years was significantly associated with autoimmune diseases (p = 0.000). The age group of 60 - 79 years was significantly associated with autoinflammatory diseases (p = 0.000). The profession as houseworkers was exclusive to females (118 cases vs. 0), and farmers and workers to males (24 cases vs. 0 and 15 cases vs. 1 case, respectively). Systemic autoimmune diseases were more frequently diagnosed in females than in males (p = 0.000). Females were 2.45 times more likely than males to have organ-specific autoimmune diseases (p = 0.001). There were no cases of monogenic autoinflammatory diseases in our study. Males were 2.04 times more likely than females to develop polygenic autoinflammatory diseases (p = 0.033). Systemic autoimmune diseases were more prevalent in patients living in urban areas (44 cases) than in those living in rural areas (26 cases) (p = 0.347). Patients living in urban areas were more likely than those living in rural areas to have organ-specific autoimmune diseases (p = 0.320). Patients living in urban areas were more likely than those living in rural areas to have polygenic autoinflammatory diseases (p = 0.469). **Conclusion:** Our study demonstrates the existence of several relevant positive associations between the age group, urban-rural status, gender and sex, and the autoimmune diseases' nosological entity, autoimmune diseases' nosological sub-entities, each of the autoimmune diseases, and autoinflammatory diseases' nosological entity, autoinflammatory diseases' nosological sub-entities, each of the autoinflammatory diseases.

Keywords

Gender, Sex, Urban-Rural, Age, Autoimmune Diseases, Autoinflammatory Diseases

1. Introduction

Autoimmune and autoinflammatory diseases are a large heterogeneous group of inflammatory diseases that have in common the chronic inflammatory process, but their clinical and biological expressions are extremely variable [1]. Autoimmune diseases are defined as all pathological manifestations linked to the involvement of effectors of the immune system, B lymphocytes, and T lymphocytes, specific to the antigens of the organism to which this system belongs (self-antigens) [2]. They are very heterogeneous and are usually classified into two groups: systemic autoimmune diseases and organ-specific autoimmune diseases [3]. As for autoinflamma-

tory diseases, they are due to an abnormality of innate immunity. There are no elevated or pathogenic autoantibodies and no activated T lymphocytes, as opposed to autoimmune diseases. They are subdivided into two groups: monogenic autoinflammatory diseases and polygenic autoinflammatory diseases [4]-[6]. However, the polygenic autoinflammatory diseases can also be subdivided into two groups: systemic polygenic autoinflammatory diseases and organ-specific polygenic autoinflammatory diseases according to their clinical phenotype [7].

Several studies have demonstrated that most autoimmune diseases occur in young adults [8] [9]. Indeed, autoimmune diseases are among the leading causes of death among young and middle-aged women in the United States. The underlying mechanism remains an open research question in the literature. However, sex-hormone upregulation and environmental factors such as endocrine-disrupting chemicals are increasingly described as being associated with the occurrence of autoimmune diseases, and thus, young adults are more likely than other age groups to be exposed [10] [11]. Monogenic autoinflammatory diseases are exceptional in sub-Saharan Africa, but cases are commonly reported in North Africa [12]. Polygenic autoinflammatory diseases such as systemic sarcoidosis occur frequently in males aged 20 - 45 years and females aged 50 - 65 years [13], with Still's disease onset at a median age of 42 years for females and 39 years for males [14].

Epidemiological data from published works suggest that sociocultural gender-based differences in autoimmune diseases and autoinflammatory diseases are a neglected area in the literature, on the one hand, and that there are more reporting biases based on confusion between sociocultural determinants (gender) and biological determinants (sex), on the other hand. Indeed, some studies report that lower education level in women, higher smoking rates in men, and environmental exposure in men are gender-related determinants associated with autoimmune diseases [15]-[17]. In addition, tertiary referral center accessibility was found to be positively correlated with poor management of sarcoidosis, an autoinflammatory disease [18].

It has long been appreciated that the majority of autoimmune diseases occur in women rather than in males. This supports that females are more susceptible to autoimmune diseases than males. Sex-based immunological and hormonal differences could contribute to the difference in disease susceptibility [10] [19] [20]. Some polygenic autoinflammatory diseases occur more frequently in females than in males, such as sarcoidosis [18] and adult-onset Still's disease [21], and some occur more frequently in males than in females, such as gout [22].

The sociocultural and environmental factors and their long-term interaction with genetic and epigenetic factors leading to immune-endocrine dysregulation may be different between urban and rural areas. These may explain the differences observed in some diseases between urban and rural areas. Indeed, the urban-rural-based differences in autoimmune and autoinflammatory diseases are less investigated. However, Allen *et al.* reported that a diagnosis peak of Type 1 diabetes, an autoimmune disease, in the third and fourth quarters among rural cases contrasted with an even quarterly distribution among urban cases [23]. In addition,

Kajdasz *et al.* demonstrated that a number of rurally linked exposures were found to be univariately associated with the development of sarcoidosis, a polygenic autoinflammatory disease [24].

Taken together, although research works have investigated the relationship between the age group, urban-rural, gender and sex-based differences and certain autoimmune and autoinflammatory diseases taken individually, there are no studies that have explored globally and exhaustively this relationship between the age group, urban-rural, gender and sex and the autoimmune diseases' nosological entity, autoimmune diseases' nosological sub-entities, each of the autoimmune diseases and autoinflammatory diseases' nosological entity, autoinflammatory diseases' nosological sub-entities, and each of the autoinflammatory diseases. In addition, these aspects are less studied in Africa, particularly in Mali.

Therefore, there is a crucial need to further explore the relationship of age, urban-rural, gender, and sex-based differences in autoimmune and autoinflammatory diseases, and furthermore to identify specific determinants associated with autoimmune and autoinflammatory diseases. Therefore, a research strategy that aims to explore these aspects would contribute to identifying new therapeutic targets and to adapting treatment and preventive strategies. We aimed in this work to determine age, urban-rural, gender, and sex-based differences in autoimmune diseases and autoinflammatory diseases in the internal medicine department at the University Hospital Center of the Point G.

2. Methods

2.1. Research Questions

The study addresses two research questions, namely: 1) Are there relevant significant associations between the age, urban-rural, gender and sex, and the autoimmune diseases' nosological entity, autoimmune diseases' nosological sub-entities, and each of the autoimmune diseases? 2) Are there relevant significant associations between the age, urban-rural, gender and sex, and autoinflammatory diseases' nosological entity, autoinflammatory diseases' nosological sub-entities, and each of the autoinflammatory diseases?

2.2. Study Design

A cross-sectional study with retrospective data collection was conducted to explore the age, urban-rural, gender, and sex-based differences in autoimmune and autoinflammatory diseases. The study strictly adhered to the cross-sectional reporting guidelines of the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) [25].

2.3. Study Setting

Bamako is the capital and largest city of Mali. Mali is a West African country, comprising 19 administrative regions. Mali is a developing country that is currently 184th out of 189, according to the United Nations Human Development

Index 2019. Mali's population is estimated at 22,395,485 inhabitants, including 47.2% of young people under the age of 15 and 49.9% of people aged 15 to 64, according to the Fifth General Census of the Population and Housing in Mali. Mali has one of the highest fertility rates in the world, with over six children per woman in 2018. Since January 2016, the guaranteed minimum salary (SMIG) has been 40,000 FCFA (US\$ 80). More than 20% of the country's population live in urban areas and more than 60% live in rural areas. In Mali, health care is organized into three levels: the district health level (community health centers and reference health centers); the second level, which represents the regional hospitals; and the third level, which is anchored by the national hospitals and university hospital centers (UHC). Among the third level is the University Hospital Center of the Point G, where the present study was conducted between January 1, 2005 and December 31, 2019, which is 15 years. It is located in Bamako. This department of internal medicine, known as a center of excellence for diagnosis and management of autoimmune and autoinflammatory diseases, is staffed by educators, researchers, and practitioner internists. A total of 6,383 patients were hospitalized during the study period.

2.4. Study Population

We included in this study all the medical records of patients hospitalized for autoimmune and/or autoinflammatory disease during the study period. We did not include in this study the outpatients, and the patients hospitalized with the diagnosis of autoimmune and/or autoinflammatory diseases in the internal medicine department at the University Hospital Center of the Point G outside the study period.

2.5. Variables

The independent study variables were the socio-demographic data, which included sex, age, profession, and residency. Autoimmune diseases' nosological entity, its nosological sub-entities, and each of the autoimmune diseases; and autoinflammatory diseases' nosological entity, its nosological sub-entities, and each of the autoinflammatory diseases are the dependent (outcome) variables, for which diagnoses were established on the basis of clinical and paraclinical data and/or validated diagnostic criteria according to the type of autoimmune and autoinflammatory diseases.

2.6. Data Collection

A pre-established survey form was designed and used to collect data on the sociodemographic and clinical characteristics. Sociodemographic variables such as sex, age, profession/gender-related occupation, residency, and clinical variables such as discharge diagnosis were collected from medical records and registry of hospitalization used for medical record identification.

2.7. Difficulties and Biases

During this study, we encountered certain problems related to the lack of infor-

mation in the medical records. Some clinical hypotheses of autoimmune and autoinflammatory diseases were not confirmed because of financial difficulties in performing specific tests.

2.8. Sampling and Sample Size

This was an exhaustive sampling of all cases of hospitalization for autoimmune and/or autoinflammatory diseases during the study period. The sample size was not calculated.

2.9. Statistical Methods

The collected data were entered into SPSS version 22 software for cleaning and analysis. Data cleaning was performed by checking and correcting for duplicates, completing missing data, and correcting outliers. We used Microsoft Excel to generate bar graphs. We conducted statistical analyses using Epi Info version 7.2 and SPSS version 22 software. We conducted univariate analysis to obtain the mean and standard deviation for quantitative data and numbers and percentages for qualitative data. In the bivariate analysis, we calculated odds ratios (OR), 95% confidence intervals (C. I.), and p-values. The outcome variables of interest for bivariate analysis were autoimmune diseases' nosological entity, autoimmune diseases' nosological sub-entities, each of the autoimmune diseases and autoinflammatory diseases' nosological entity, autoinflammatory diseases' nosological sub-entities, and each of the autoinflammatory diseases. The categorical independent variables of interest were age group, sex, profession, and residency. The sex refers to the biological male/female differences, and the gender refers to social roles typically associated with the sex of a patient like profession/occupation, in other words, the occupational male/female differences. The Chi-square (uncorrected and corrected) and Fisher's exact tests were used to assess the statistical significance and strength of the associations between the categorical independent variables and the outcome variables. A two-tailed p-value < 0.05 was retained and considered as statistically significant.

2.10. Ethical Consideration

According to the Helsinki guideline, research involving human subjects should be conducted ethically, with the well-being of the subject taking priority over scientific or societal interests. Our research study aimed to provide cross-sectional data on the relationship between age group, urban-rural, gender and sex-based differences, and all autoimmune and autoinflammatory diseases in the internal medicine department involving human subjects. However, we used secondary data from patients' medical records (sociodemographic and clinical data) and did not use biological specimens.

In addition, the study was retrospective, and all data were extracted anonymously from the medical records and registry of hospitalization. Therefore, patients' informed consent was not required.

Given the nature of the study, formal ethical approval from an ethics committee was not sought. However, formal permission to conduct this study was obtained from the General Director of University Hospital Center of the Point G. The medical records and registry of hospitalization were returned to the archive room immediately after exploitation.

3. Results

3.1. Characteristics of the Study Participants

During a fifteen-year study period, 331 cases of autoimmune diseases and autoinflammatory diseases, including 07 cases of associations, were noted from 317 medical records. These were 291 cases of autoimmune diseases and 40 cases of autoinflammatory diseases. Socio-demographic data are illustrated in the supplementary **Figure 1**. Out of the 317 medical records included in the study, females represented 65.0% of cases with a sex ratio of 0.54. The age group of 20 - 39 years accounted for 50.2% of the study population; the mean age of patients was 35.3 ± 16.3 years; and the extreme ages were 07 and 79 years. Houseworkers were found in 37.2% of cases. Patients came from urban areas in 65.5% of cases.

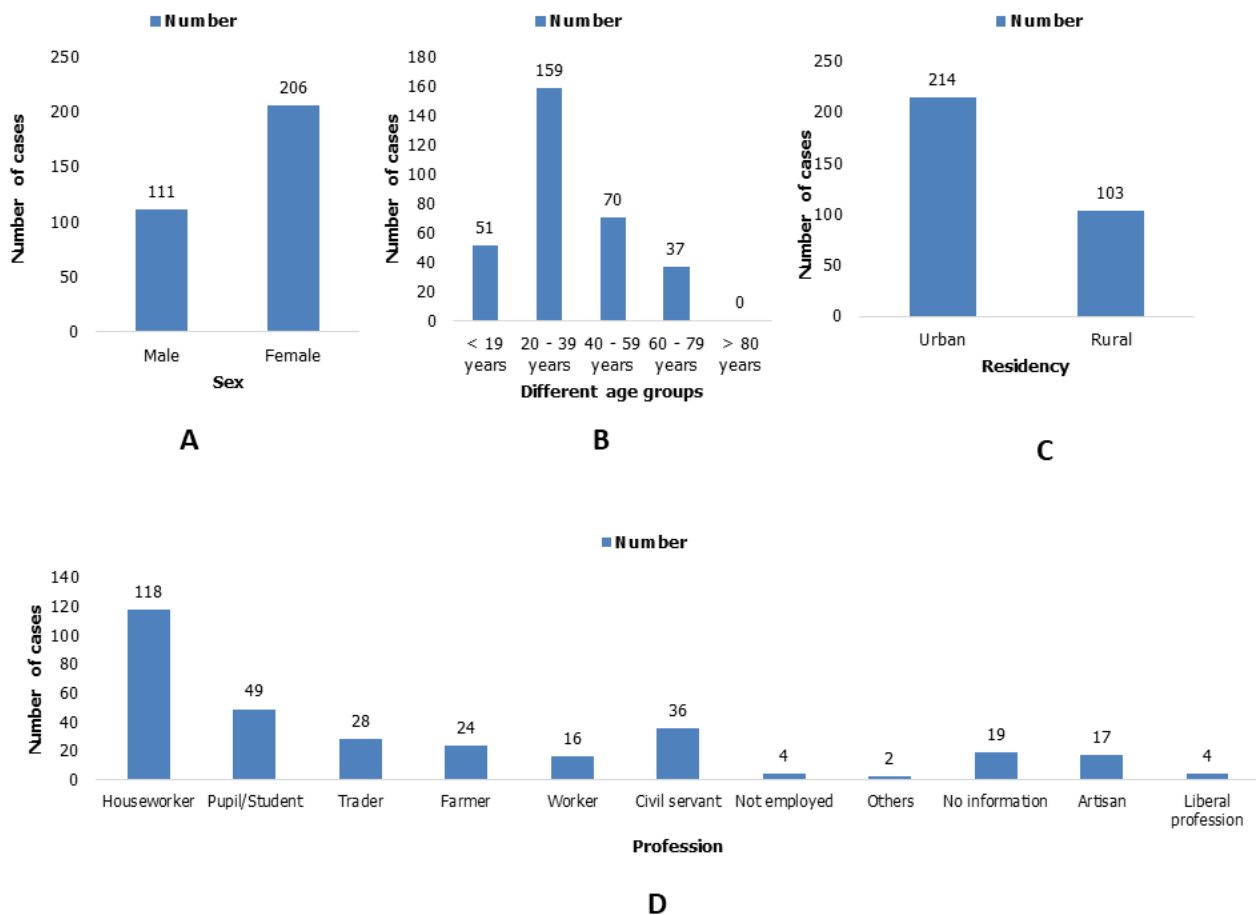


Figure 1. Distribution of patients according to sociodemographic data such as sex (A), age groups (B), residency (C), and profession (D).

3.2. Age-Based Differences in Autoimmune and Autoinflammatory Diseases

Table 1 summarizes the comparison of patients between the different age groups and the autoimmune and autoinflammatory diseases. The age group of 20 - 39 years was significantly associated with autoimmune diseases (153 cases; OR = 5.02; 95% CI = 2.01 - 12.57; $p = 0.000$). The age group of 60 - 79 years was significantly associated with autoinflammatory diseases (16 cases; OR = 8.13; 95% CI = 3.75 - 17.61; $p = 0.000$).

Table 1. Distribution of patients according to age groups and autoimmune and autoinflammatory diseases.

Age group	Autoimmune diseases			Autoinflammatory diseases		
	n (%)	OR (95% CI)	p-value	n (%)	OR (95% CI)	p-value
<19 years	47 (16.5)	1.38 (0.46 - 4.13)	0.560	5 (12, 5)	0.72 (0.27 - 1.93)	0.509
20 - 39 years	153 (53.7)	5.02 (2.01 - 12.57)	0.000	8 (20, 0)	0.21 (0.10 - 0.47)	0.000
40 - 59 years	61 (21.4)	0.70 (0.31 - 1.58)	0.385	11 (27, 5)	1.40 (0.66 - 2.97)	0.377
60 - 79 years	24 (8.4)	0.13 (0.06 - 0.30)	0.000	16 (40, 0)	8.13 (3.75 - 17.61)	0.000

3.3. Gender-Based Differences in Autoimmune and Autoinflammatory Diseases

Comparison of patients by sex and profession are mentioned in Supplement **Figure 2**. The profession of houseworker was exclusive to females (118 cases vs. 0), while farmers and workers were predominantly male (24 cases vs. 0 and 15 cases vs. 1 case, respectively). **Table 2** shows the comparison of patients by profession and autoimmune and autoinflammatory diseases. There was no significant correlation between houseworkers and autoimmune diseases (109 houseworkers; OR = 1.58; 95% CI = 0.71 - 3.55; $p = 0.261$), or between farmers and autoimmune diseases (19 farmers; OR = 0.39; 95% CI = 0.13 - 1.12; $p = 0.080$). Autoinflammatory diseases occurred more frequently in houseworkers (9 houseworkers; OR = 0.45; 95% CI = 0.21 - 0.98; $p = 0.039$). Farmers were 2.54 times more likely to develop autoinflammatory diseases than other professions (6 farmers; OR = 2.54; 95% CI = 0.94 - 6.84; $p = 0.114$).

Table 2. Distribution of patients according to profession and autoimmune and autoinflammatory diseases.

Profession	Autoimmune diseases		Autoinflammatory diseases	
	Autoimmune diseases, n (%)	Not autoimmune diseases, n (%)	Autoinflammatory diseases, n (%)	Not autoinflammatory diseases, n (%)
Houseworker	109 (92.4)	9 (7.6)	9 (7.6)	109 (89.8)

Continued

Pupil/Student	45 (91.8)	4 (8.2)	5 (10.2)	44 (89.8)
Trader	26 (92.9)	2 (7.1)	2 (7.1)	26 (92.9)
Farmer	19 (79.2)	5 (20.8)	6 (25.0)	18 (75.0)
Worker	12 (75.0)	4 (25.0)	5 (31.3)	11 (68.8)
Civil servant	32 (88.9)	4 (11.1)	6 (16.7)	30 (83.3)
Not employed	4 (100)	0 (0)	0 (0)	4 (100)
Others	2 (100)	0 (0)	0 (0)	2 (100)
No information	18 (94.7)	1 (5.3)	1 (5.3)	18 (94.7)
Artisan	14 (82.4)	3 (5.3)	5 (29.4)	12 (70.6)
Liberal profession	4 (100)	0 (0)	1 (25.0)	3 (75.0)

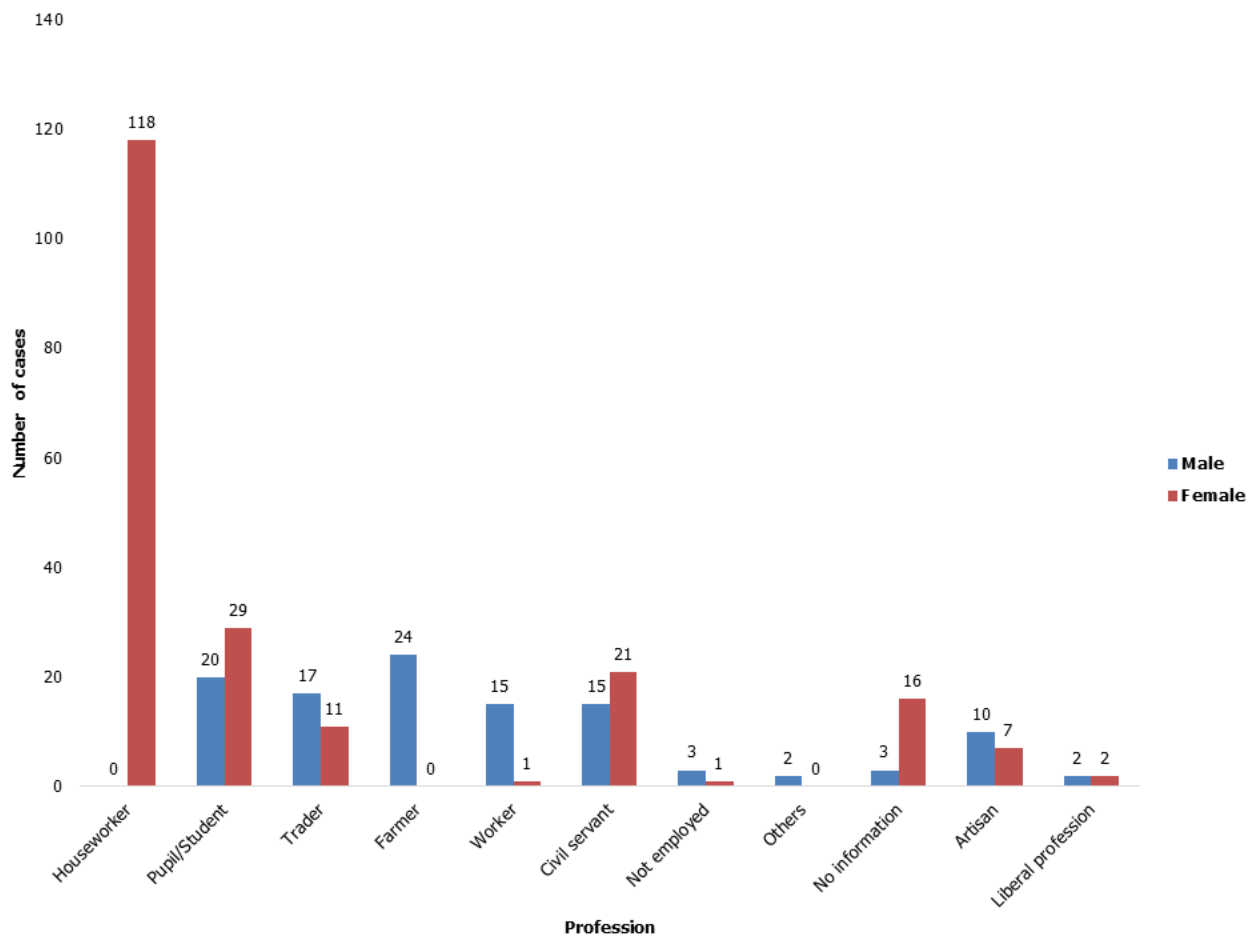


Figure 2. Distribution of patients with autoimmune and autoinflammatory diseases according to sex and profession.

3.4. Sex-Based Differences in Autoimmune and Autoinflammatory Diseases

Table 3 summarizes the comparison of patients between the sex and the autoim-

mune diseases. Systemic autoimmune diseases were more frequently diagnosed in females than in males (63 cases vs. 7 cases; OR = 0.15; 95% CI = 0.07 - 0.35; $p = 0.000$). The systemic autoimmune diseases found were dominated by systemic lupus erythematosus (3 males vs. 40 females, $p = 0.000$) and rheumatoid arthritis (3 males vs. 13 females, $p = 0.162$). Females were 2.45 times more likely than males to have organ-specific autoimmune diseases (90 cases vs. 131 cases; OR = 2.45; 95% CI = 1.41 - 4.27; $p = 0.001$). Type 1 diabetes (64 males vs. 77 females; OR = 2.28; 95% CI = 1.43 - 3.65; $p = 0.001$) and Graves' disease (10 males vs. 38 females, OR = 0.44; 95% CI = 0.20 - 0.92; $p = 0.025$) were the most common organ-specific autoimmune diseases.

Table 3. Distribution of patients according to sex and autoimmune diseases.

Autoimmune diseases	Sex		Male-to-female ratio	OR (95% CI)	p-value
	Male, n = 101 n (%)	Female, n = 206 n (%)			
Systemic autoimmune diseases	7 (6.31)	63 (30.58)	0.11	0.15 (0.07 - 0.35)	0.000
Systemic lupus erythematosus	3 (2.70)	40 (19.42)	0.07	0.12 (0.03 - 0.38)	0.000
Systemic scleroderma	1 (0.90)	3 (1.46)	0.33	0.61 (0.18 - 5.98)	1.000
Dermato-polymyositis	0 (0.00)	1 (0.49)	0	-	1.000
Rheumatoid arthritis	3 (2.70)	13 (6.31)	0.23	0.41 (0.12 - 1.48)	0.162
Sharp syndrome/mixed connective tissue diseases ^a	0 (0.00)	6 (2.91)	0	-	0.095
Rheumatoid arthritis + Systemic lupus erythematosus	0 (0.00)	1 (0.49)	0	-	
Rheumatoid arthritis + Systemic lupus erythematosus + Dermato-polymyositis + Systemic scleroderma	0 (0.00)	1 (0.49)	0	-	0.529
Systemic lupus erythematosus + Systemic scleroderma	0 (0.00)	4 (1.94)	0	-	
Systemic auto-immune vasculitis	0 (0.00)	0 (0.00)	-	-	-
Organ-specific autoimmune diseases	90 (81.08)	131 (63.59)	0.69	2.45 (1.41 - 4.27)	0.001
Type 1 diabete	64 (57.66)	77 (37.38)	0.83	2.28 (1.43 - 3.65)	0.001
Autoimmune polyendocrinopathies ^a	1 (0.90)	1 (0.49)	1	1.86 (0.12 - 30.08)	1.000
De Quervain's thyroiditis	0 (0.00)	1 (0.49)	0	-	1.000
Graves' disease	10 (9.01)	38 (18.45)	0.26	0.44 (0.20 - 0.92)	0.025
Guillain Barre syndrome	4 (3.60)	3 (1.46)	1.33	2.55 (0.56 - 11.62)	0.245

Continued

Multiple sclerosis	0 (0.00)	1 (0.49)	0	-	1.000
Myasthenia gravis	3 (2.70)	0 (0.00)	-	-	0.042
Autoimmune hepatitis	1 (0.90)	0 (0.00)	-	-	0.350
Autoimmune hemolytic anemia	2 (1.80)	8 (3.88)	0.25	0.45 (0.09 - 2.17)	0.499
Immunological thrombocytopenic purpura	0 (0.00)	1 (0.49)	0	-	1.000
Biermers' disease	6 (5.41)	2 (0.97)	3	5.82 (1.56 - 29.38)	0.024

Autoimmune polyendocrinopathies^a: Graves' disease + Addison's diseases (2 cases).

Comparison of patients by sex and autoinflammatory diseases is mentioned in **Table 4**. There were no cases of monogenic autoinflammatory diseases in our study. Males were 2.04 times more likely than females to develop polygenic autoinflammatory diseases (20 cases vs. 20 cases; OR = 2.04; 95% CI = 1.05 - 3.99; $p = 0.033$). Systemic polygenic autoinflammatory diseases were 3.19 times more likely to be found in males than in females (5 cases vs. 3 cases; OR = 3.19; 95% CI = 0.75 - 13.61; $p = 0.134$). These systemic polygenic autoinflammatory diseases were dominated by systemic non-autoimmune vasculitis (5 cases vs. 1 case; OR = 9.67; 95% CI = 1.12 - 83.83; $p = 0.021$). Organ-specific polygenic autoinflammatory diseases were more common in females than in males (15 cases vs. 17 cases; OR = 1.74; 95% CI = 0.83 - 3.63; $p = 0.138$). Among the organ-specific polygenic autoinflammatory diseases, chronic inflammatory rheumatism (11 cases vs. 11 cases; $p = 0.127$), gout as microcrystalline arthropathies (8 cases vs. 8 cases; $p = 0.197$), and spondylarthropathies (2 cases vs. 1 case; $p = 0.281$), and chronic inflammatory bowel disease (4 cases vs. 6 cases; $p = 0.000$) were more prevalent.

3.5. Urban-Rural Based Differences in Autoimmune and Autoinflammatory Diseases

Table 5 summarizes the comparison of patients between the residency and autoimmune diseases. Systemic autoimmune diseases were more prevalent in patients living in urban areas at the time of diagnosis (44 cases) than in patients living in rural areas (26 cases), (OR = 0.77; 95% CI = 0.44 - 1.33; $p = 0.347$). There were no statistically significant differences between patients living in urban areas and patients living in rural areas in regards to systemic autoimmune diseases such as systemic lupus erythematosus (28 cases vs. 15 cases; $p = 0.719$) and rheumatoid arthritis (11 cases vs. 15 cases; $p = 0.913$). Patients living in urban areas were more likely than patients living in rural areas to have organ-specific autoimmune diseases (153 cases vs. 68 cases; OR = 1.29; 95% CI = 0.78 - 2.14; $p = 0.320$). Type 1 diabetes (101 patients living in urban areas vs. 40 patients living in rural areas; $p = 0.161$) and Graves' disease (35 patients living in urban areas vs. 23 patients living in rural areas; $p = 0.385$) were the most common organ-specific autoimmune diseases.

Table 4. Distribution of patients according to diseases, sex, and autoinflammatory.

Autoinflammatory diseases	Sex		Male-to-female ratio	OR (95% CI)	p-value
	Male, n = 101 n (%)	Female, n = 206 n (%)			
Monogenic autoinflammatory diseases	0 (0.00)	0 (0.00)	-	-	-
Polygenic autoinflammatory diseases	20 (18.02)	20 (9.71)	1	2.04 (1.05 - 3.99)	0.033
Systemic polygenic autoinflammatory diseases	5 (4.50)	3 (1.46)	1.66	3.19 (0.75 - 13.61)	0.134
Systemic non-autoimmune vasculitis	5 (4.50)	1 (0.49)	5	9.67 (1.12 - 83.83)	0.021
Horton's disease	2 (1.80)	0 (0.00)	-	-	0.122
Periarthritis nodosa	1 (0.90)	0 (0.00)	-	-	0.350
Vasculitis of undetermined origin	0 (0.00)	1 (0.49)	0	-	0.650
Burger angitis	1 (0.90)	0 (0.00)	-	-	0.350
Other systemic non-autoimmune vasculitis	2 (1.80)	0 (0.00)	2	-	0.122
Burger angitis	1 (0.90)	0 (0.00)	-	-	0.122
leukocytoclassical vascularitis	1 (0.90)	0 (0.00)	-	-	0.122
Systemic sarcoidosis	0 (0.00)	1 (0.49)	0	-	1.000
Still's disease	0 (0.00)	1 (0.49)	0	-	1.000
Organ-specific polygenic autoinflammatory diseases	15 (13.31)	17 (8.25)	0.88	1.74 (0.83 - 3.63)	0.138
Chronic inflammatory rheumatism	11 (9.91)	11 (5.34)	1	1.95 (0.82 - 4.65)	0.127
Pseudo rheumatoid arthritis	1 (0.90)	0 (0.00)	-	-	0.350
Microcrystalline arthropathies	8 (7.21)	8 (3.88)	1	1.92 (0.70 - 5.27)	0.197
Gout	8 (7.21)	8 (3.88)	1	1.92 (0.70 - 5.27)	0.197
Chondrocalcinosis	0 (0.00)	0 (0.00)	-	-	-
Spondylarthropathies	2 (1.80)	1 (0.49)	2	3.76 (0.34 - 41.95)	0.281
Reactive arthritis	1 (0.90)	0 (0.00)	-	-	-
Psoriatic rheumatism	0 (0.00)	1 (0.49)	0	-	0.281
Ankylosing spondylitis	1 (0.90)	0 (0.00)	-	-	-
Other chronic inflammatory diseases	2 (1.80)	0 (0.00)	-	-	0.543
Juvenile idiopathic arthritis	0 (0.00)	1 (0.49)	0	-	1.000
Jaccoub's arthropathy	0 (0.00)	1 (0.49)	0	-	-

Continued

Chronic inflammatory bowel disease	4 (3.60)	6 (2.91)	0.67	1.25 (0.34 - 4.51)	0.000
Crohn's diseases	1 (0.90)	1 (0.49)	1	1.85 (0.12 - 30.08)	1.000
Ulcerative colitis	3 (2.70)	5 (2.43)	0.67	1.12 (0.26 - 4.76)	1.000

Table 5. Distribution of patients according to residency and autoimmune diseases.

Autoimmune diseases	Residency		OR (95% CI)	P-value
	Urban, n = 214 n (%)	Rural, n = 103 n (%)		
Systemic autoimmune diseases	44 (20.56)	26 (25.24)	0.77 (0.44 - 1.33)	0.347
Systemic lupus erythematosus	28 (13.08)	15 (14.56)	0.88 (0.44 - 1.74)	0.719
Systemic scleroderma	1 (0.47)	3 (2.91)	0.16 (0.02 - 1.52)	0.102
Dermato-polymyositis	0 (0.00)	1 (0.97)	-	0.325
Rheumatoid arthritis	11 (5.14)	5 (4.85)	1.06 (0.36 - 3.14)	0.913
Sharp syndrome/mixed connective tissue diseases ^a	5 (2.34)	1(0.97)	2.44 (0.28 - 21.16)	0.366
Systemic auto-immune vasculitis	0 (0.00)	0 (0.00)	-	-
Organ-specific autoimmune diseases	153 (71.50)	68 (66.02)	1.29 (0.78 - 2.14)	0.320
Type 1 diabete	101 (47.20)	40 (38.83)	1.41 (0.87 - 2.27)	0.161
Autoimmune polyendocrinopathies ^b	1 (0.47)	1(0.97)	0.48 (0.03 - 7.73)	0.545
De Quervain's thyroiditis	1 (0.47)	0(0.00)	-	1.000
Graves' disease	35 (16.36)	23 (12.62)	1.35 (0.75 - 2.69)	0.385
Guillain Barre syndrome	5 (2.34)	2 (1.94)	1.21 (0.23 - 6.33)	1.000
Multiple sclerosis	1 (0.47)	0 (0.00)	-	1.000
Myasthenia gravis	1 (0.47)	2 (1.94)	0.24 (0.02 - 2.65)	0.247
Autoimmune hepatitis	1 (0.47)	0 (0.00)	-	1.000
Autoimmune hemolytic anemia	4 (1.87)	6 (5.83)	0.31 (0.08 - 112)	0.123
Immunological thrombocytopenic prupura	0 (0.00)	1(0.97)	-	0.325
Biermers' disease	5 (2.34)	3 (2.91)	0.80 (0.19 - 3.40)	0.718

Sharp syndrome/mixed connective tissue diseases^a: Systemic lupus erythematosus + rheumatoid arthritis (1 case); systemic lupus erythematosus + rheumatoid arthritis + dermato-polymyositis (DPM) + systemic scleroderma (1 case); systemic lupus erythematosus + systemic scleroderma (4 cases); Autoimmune polyendocrinopathies^b: Graves' disease + Addison's disease (2 cases).

Comparison of patients between the residency and the autoinflammatory diseases are mentioned in **Table 6**. Patients living in urban areas were more likely than patients living in rural areas to have polygenic autoinflammatory diseases (25 cases vs. 15 cases; OR = 0.78; 95% CI = 0.39 - 1.54; p = 0.469). There were no statistically significant differences between patients living in urban areas and patients living in rural areas regarding systemic polygenic autoinflammatory diseases (4 cases vs. 4 cases; p = 0.281). These were dominated by systemic non-autoimmune vasculitis (3 patients living in urban areas vs. 3 patients living in rural areas; p = 0.394). Organ-specific polygenic autoinflammatory diseases were more frequent in patients living in urban areas than in patients living in rural areas (21 cases vs. 11 cases; OR = 0.91; 95% CI = 0.42 - 1.97; p = 0.810). Among the organ-specific polygenic autoinflammatory diseases, chronic inflammatory rheumatism (16 patients living in urban areas vs. 6 patients living in rural areas; p = 0.588): gout as microcrystalline arthropathies (11 patients living in urban areas vs. 5 patients living in rural areas; p = 0.913), spondylarthropathies (2 patients living in urban areas vs. 1 patient living in rural areas; p = 1.000), and chronic inflammatory bowel disease (5 patients living in urban areas vs. 5 patients living in rural areas; p = 0.391) were more represented.

Table 6. Distribution of patients according to residency and autoinflammatory diseases.

Autoinflammatory diseases	Residency		OR (95% CI)	P-value
	Urban, n = 214 n (%)	Rural, n = 103 n (%)		
Monogenic autoinflammatory diseases	0 (0.00)	0 (0.00)	-	-
Polygenic autoinflammatory diseases	25 (11.68)	15 (14.56)	0.78 (0.39 - 1.54)	0.469
Systemic polygenic autoinflammatory diseases	4 (1.87)	4 (3.88)	0.47 (0.12 - 1.92)	0.281
Systemic non-autoimmune vasculitis	3 (1.40)	3 (2.91)	0.47 (0.09 - 2.39)	0.394
Horton's disease	2 (0.93)	0 (0.00)	-	1.000
Periarthritis nodosa	0 (0.00)	1 (0.97)	-	0.325
Vasculitis of undetermined origin	0 (0.00)	1 (0.97)	-	0.325
Other systemic non-autoimmune vasculitis	1 (0.47)	1 (0.97)	0.48 (0.03 - 7.73)	0.545
<i>Burger angitis</i>	0 (0.00)	1 (0.97)	-	-
<i>Leucytoclassic vascularitis</i>	1 (0.47)	0 (0.00)	-	-
Systemic sarcoidosis	1 (0.47)	0 (0.00)	-	1.000
Still's disease	0 (0.00)	1 (0.97)	-	0.325
Organ-specific polygenic autoinflammatory diseases	21 (9.81)	11 (10.68)	0.91 (0.42 - 1.97)	0.810
Chronic inflammatory rheumatism	16 (7.48)	6 (5.83)	1.31 (0.50 - 3.44)	0.588
Pseudo rheumatoid arthritis	1 (0.47)	0 (0.00)	-	1.000

Continued

Microcrystalline arthropathies	11 (5.14)	5 (4.85)	1.06 (0.36 - 3.14)	0.913
Gout	11 (5.14)	5 (4.85)	1.06 (0.36 - 3.14)	0.913
Chondrocalcinosis	0 (0.00)	0 (0.00)	-	-
Spondylarthropathies	2 (0.93)	1 (0.97)	0.96 (0.86 - 10.74)	1.000
Reactive arthritis	0 (0.00)	1 (0.97)	-	-
Psoriatic rheumatism	1 (0.47)	0 (0.00)	-	0.694
Ankylosing spondylitis	1 (0.47)	0 (0.00)	-	-
Other chronic inflammatory diseases	2 (0.93)	0 (0.00)	-	1.000
Juvenile idiopathic arthritis	1 (0.47)	0 (0.00)	-	-
Jaccoub's arthropathy	1 (0.47)	0 (0.00)	-	1.000
Chronic inflammatory bowel disease	5 (2.34)	5 (4.85)	0.47 (0.13 - 1.66)	0.391
Crohn's diseases	1 (0.47)	1 (0.97)	0.48 (0.03 - 7.73)	0.545
Ulcerative colitis	4 (1.87)	4 (3.88)	0.47 (0.12 - 1.92)	0.281

4. Discussion

4.1. Main Findings

The result from our 15-year cross-sectional study revealed the existence of age-, urban-rural, gender-, and sex-based differences in autoimmune and autoinflammatory diseases. To our knowledge, it is the first study that has explored these aspects globally and exhaustively.

4.2. Characteristics of the Study Participants

This study showed that the overall hospital frequency of autoimmune diseases and autoinflammatory diseases was slightly low, females were more represented than males, and study populations were younger. These results are in line with findings from previous studies [26]-[28]. In addition, autoimmune diseases and autoinflammatory diseases are part of rare diseases except for some cases such as rheumatoid arthritis and autoimmune thyroiditis [29] [30].

4.3. Age-Based Differences in Autoimmune and Autoinflammatory Diseases

Autoimmune diseases are defined as all pathological manifestations linked to the involvement of effectors of the immune system, B lymphocytes and T lymphocytes, specific to the antigens of the organism to which this system belongs (self-antigens). In contrast, autoinflammatory diseases are due to an abnormality of innate immunity [2] [4]. To our knowledge, there are no epidemiological data from published work seeking age group-, urban-rural-, gender-, and sex-based differences in these two major nosological entities and their sub-entities: autoimmune diseases (systemic autoimmune diseases and organ-specific autoimmune diseases) and autoinflammatory diseases (monogenic autoinflammatory diseases and polygenic au-

toinflammatory diseases), but several pieces of evidence studied individually different autoimmune and autoinflammatory diseases. The age group of 20 - 39 years was significantly associated with autoimmune diseases; this is in concordance with previous studies [8] [9] [31]. Several studies showed that certain autoinflammatory diseases were more likely to be diagnosed in the elderly than in other age groups, in accordance with our study [13] [32]. In contrast, certain autoinflammatory diseases were more often diagnosed in younger old years [14] [13].

4.4. Gender-Based Differences in Autoimmune and Autoinflammatory Diseases

Gender generally refers to socially constructed roles, behaviors, and identities of women, men, and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact, and how power is distributed in society [33].

In our study, the profession of houseworker was exclusively for females, and farmer and worker for males, which strongly indicates that some occupations are devoted either to males or to females. There was a significant correlation between houseworker and autoinflammatory diseases. What are the potential underlying reasons? To determine these potential underlying reasons, such as exposure to specific indoor environmental agents, would provide valuable context and direction for future research. In other words, the houseworker-specific determinants associated with autoinflammatory diseases should be further explored in large cohort studies.

4.5. Sex Differences in Autoimmune and Autoinflammatory Diseases

Sex generally refers to a set of biological attributes that are associated with physical and physiological features (e.g., chromosomal genotype, hormonal levels, internal and external anatomy). A binary sex categorization (male/female) is usually designated at birth (“sex assigned at birth”), most often based solely on the visible external anatomy of a newborn [33].

In our study, the systemic autoimmune diseases were more frequently diagnosed in females than in males. The systemic autoimmune diseases found were dominated by systemic lupus erythematosus and rheumatoid arthritis. Multiple studies found that systemic lupus erythematosus and rheumatoid arthritis were more prevalent in females than in males; these results parallel our findings [15] [34]-[36]. The females were more likely than the males to have the organ-specific autoimmune diseases. Type 1 diabetes and Graves’ disease were the most common of the organ-specific autoimmune diseases. Males were 2.89 times more likely to develop type 1 diabetes than females in our study, consistent with some previous studies [37] [38]. In contrast, Wändell *et al.* report no significant sex difference in type 1 diabetes in children 0 - 14 years of age [37]. This discrepancy may be explained by methodological approaches, notably the study population is stratified

by age group in this study, but not in our studies [37].

In our study, there were no cases of monogenic autoinflammatory diseases. The males were 2.04 times more likely than the females to have polygenic autoinflammatory diseases. Furthermore, males were 3.19 times more likely to develop systemic polygenic autoinflammatory diseases than females, although this increase was not statistically significant. These systemic polygenic autoinflammatory diseases were dominated by systemic non-autoimmune vasculitis. Several epidemiological data found that some systemic non-autoimmune vasculitides, such as giant cell arteritis, are more frequently found in females than in males [39] [40]. However, in our study, males were more likely to have had giant cell arteritis compared to females. These differences may reflect the participant inclusion criteria and the site of the study, which were hospital-based, monocentric with exhaustive recruitment of all autoimmune and autoinflammatory cases in our study.

Organ-specific polygenic autoinflammatory diseases were more common in females than in males. Among the organ-specific polygenic autoinflammatory diseases, gout as microcrystalline was the most prevalent. Males were 1.92 times more likely to have gout compared to females, as was found in this study [22].

4.6. Urban-Rural Based Differences in Autoimmune and Autoinflammatory Diseases

The systemic autoimmune diseases, in our study, were more prevalent in patients living in urban areas than in patients living in rural. There were no statistically significant differences between patients living in urban areas and patients living in rural areas in regards to systemic autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis, these results are not in line with findings from previous studies. Gergianaki *et al.* showed that the risk of systemic lupus erythematosus in urban areas was 2.08 times higher than in rural areas [41]. Then, Iltchev P *et al.* found that rheumatoid arthritis was more than twice as common in urban areas as in rural areas [42]. Both studies were population-based studies with large sample sizes, whereas ours was a hospital-based study, which may explain this contrast.

The patients living in urban areas were more likely than the patients living in rural areas to have organ-specific autoimmune diseases. The patients living in urban areas were not more likely to have had type 1 diabetes and Graves' disease, compared to patients living in rural areas, in accordance with literature data [43] [44].

The patients living in urban areas were more likely than the patients living in rural areas to develop polygenic autoinflammatory diseases. Systemic polygenic autoinflammatory diseases were dominated by systemic non-autoimmune vasculitis, among which giant cell arteritis was prevalent. This population-based study found that giant cell arteritis was significantly more frequent in patients living in urban areas than in patients living in rural areas, consistent with our study findings [45].

Organ-specific polygenic autoinflammatory diseases were more frequent in pa-

tients living in urban areas than in patients living in rural areas. The organ-specific polygenic autoinflammatory diseases were dominated by chronic inflammatory rheumatism, including gout as microcrystalline disease and chronic inflammatory bowel disease. Dehlin *et al.* studied the incidence and prevalence of gout in Western Sweden, in which there was no significant difference in the prevalence of gout in rural compared to urban areas; this is in concordance with our study findings [46].

4.7. Study Limitations

Our study has limitations. Firstly, the patients were followed as outpatients in the internal medicine department, and the patients treated in other departments at the University Hospital Center of the Point G and other health structures for autoimmune and autoinflammatory disease, which may have led to under-ascertainment in the latter. A second limitation is that we had not confirmed the autoimmune and autoinflammatory diseases in certain patients because of socio-economic status. Thus, the patients did not undergo certain specific para-clinical examinations to confirm the diagnosis, which may cause confounding biases. Finally, there is a referral bias because the study was conducted at a single tertiary referral center; the patient population may not be representative of the general population, which may hamper generalizability.

Elsewhere, there was serious difficulty in comparing our findings with others, notably the two heterogeneous nosological entities and their nosological sub-entities. Whereas, it is well known that diseases with similar immune-genetic and pathophysiological characteristics are regrouped as a nosological entity and sub-nosological entities [1]. Similar therapeutic targets, diagnostic and therapeutic tools, diagnostic and therapeutic strategies, and preventive medicine strategies for these nosological entities and sub-nosological entities could be developed. In this context, it is crucial to determine globally the distribution of these two nosological entities and their nosological sub-entities, as well as each of the diseases taken individually, and to also estimate the burden of these diseases in order to adapt public health actions, particularly in low-income countries.

4.8. Study Strengths

This study contains several strengths. First, it is a long-term observational study with an exhaustive method of sampling of all cases of autoimmune and autoinflammatory diseases. Second, consent procedures were not required for enrollment, therefore minimizing bias and slightly increasing the generalizability of the results. Third, our study demonstrates the scope of the problem regarding age, urban-rural, gender, and sex-based variations in autoimmune and autoinflammatory diseases, and we believe that our data provide sufficient grounds for a reexamination of the correlation between the age-, urban-rural-, gender-, and sex-specific determinants and the autoimmune and autoinflammatory diseases. And finally, our study provided an analytical epidemiological overview of these two heterogeneous nosological entities and their nosological sub-entities, as well as each

of the diseases taken individually, which could allow i) health decision-makers to appreciate globally the distribution and to eventually estimate the burden of these diseases, then to adapt preventive medicine strategies by prioritizing the target population by age group, sex, living in urban or rural settings, and gender-related occupation regarding each of the autoimmune and autoinflammatory diseases, and the disease management strategies by prioritizing the acquisition of reference diagnostic tools and reference specific treatments of each autoimmune and autoinflammatory disease, ii) clinicians to integrate these findings into the diagnostic approach, notably anamnestic clues, iii) researchers to pursue the investigation of specific determinants of these socio-demographic factors associated with the autoimmune and autoinflammatory diseases.

4.9. Perspectives

The Malian registry of autoimmune and autoinflammatory diseases should receive more funding and be better structured in order to provide a large multi-center cohort study necessary to identify the significant correlations between age group-, urban-rural-, gender-, and sex-based differences, and also extend to ethnicity, seasonality, geographic, and occupational variations in autoimmune and autoinflammatory diseases. In addition, it should allow for more exploration of its specific determinants associated with the development of these autoimmune and autoinflammatory diseases.

5. Conclusion

Autoimmune diseases are significantly prevalent in young adults, while autoinflammatory diseases are prevalent in the elderly. Gender-related occupations are found among some professions such as houseworker, farmer, and worker. Systemic autoimmune diseases are more frequently diagnosed in females than in males. Females are more likely than males to have organ-specific autoimmune diseases. There are no cases of monogenic autoinflammatory diseases in our study. Males are more likely than females to have polygenic autoinflammatory diseases. Furthermore, males are more likely to develop systemic polygenic autoinflammatory diseases than females. Organ-specific polygenic autoinflammatory diseases were more common in females than in males. Systemic autoimmune diseases are more prevalent in patients living in urban areas at the time of diagnosis than in patients living in rural areas. Patients living in urban areas are more likely than patients living in rural areas to have organ-specific autoimmune diseases. Patients living in urban areas are more likely than patients living in rural areas to develop polygenic autoinflammatory diseases. There were no statistically significant differences between patients living in urban areas and patients living in rural areas regarding systemic polygenic autoinflammatory diseases. Organ-specific polygenic autoinflammatory diseases were more frequent in patients living in urban areas than in patients living in rural areas. Upon studying the age-, urban-rural-, gender-, and sex-based differences in autoimmune and autoinflammatory diseases, specific determinants

associated with the development of autoimmune and autoinflammatory diseases should be further explored.

Conflicts of Interest

The authors declare that they have no competing interests.

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