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Adherence, Burden, and Morbidity in Adults with Chronic Diseases in the Dominican Republic: A Cross-sectional Study in a Tertiary-level Hospital (A-CaMo II)

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Abstract

Introduction: *Pharmacological adherence is a key factor in managing chronic non-communicable diseases (NCDs), so its efficacy concerning new therapies emerges as an essential consideration. Despite efforts, adherence rates vary widely, highlighting the complexity of the problem. Non-adherence affects treatment effectiveness and increases patient burden and medical costs. Understanding the interplay between burden, morbidity, and adherence is crucial for adapting health strategies.*

Objective: *This study aims to measure pharmacological adherence, burden, and morbidity among patients with chronic diseases in the Dominican Republic, emphasizing the interplay between these dimensions.*

Methods: *Data were collected using a cross-sectional design at the Centro Médico de Diabetes, Obesidad y Especialidades (CEMDOE) in Santo Domingo during August 2023. Patient interviews were conducted using standardized tools, including the Medication Adherence Reasons Scale (MAR-Scale) and the Disease Burden Morbidity Assessment (DBMA). Non-probability convenience sampling yielded a sample of 384 patients who met the inclusion criteria. Significant statistical analysis included an ordinal regression analysis correlating medication adherence with disease burden.*

Results: *Among the patients studied, the ordinal regression analysis unveiled a significant correlation ($p = 0.001$) between nonadherence and disease burden, indicating a 0.29 ± 0.09 unit increase in burden for every one-point decrease in adherence score. Patients with private health insurance and higher education levels exhibited more excellent adherence rates (65.97% and 63.89%, respectively), with a substantial portion also reporting a burden score ≥ 5 (70.07% and 70.42%, respectively). Moreover, the study population experienced a significant burden of multimorbidity (88.8%), with hypertension displaying the lowest burden (1.63 ± 1.13) despite its prevalence (76.76%).*

Conclusion: *Despite the limitations, common reasons for non-adherence were identified, and significant disease burdens were observed, particularly in osteoarthritis, cancer, and rheumatoid arthritis. Notably, a positive association was found between adherence and disease burden, underlining the importance of adherence in chronic disease management. Health disparities affecting access to medication and patient education were observed, highlighting the need for further research and intervention. The combined use of a scale that integrates both the DBMA and the MAR-Scale, in which adherence, burden, and morbidity are investigated simultaneously for each disease, would allow for a more comprehensive approach to all three characteristics regardless of which disease is included in the scales separately.*

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Introduction

Could pharmacological adherence be more efficient than the development of new therapies? This question raises a profound reflection on the health landscape in the context of chronic non-communicable diseases (NCDs). Chronic diseases lasting three months or more pose a constant challenge marked by

non-adherence to prescribed pharmacological treatment (National Center for Chronic Disease Prevention and Health Promotion, 2022; NCI Dictionary of Cancer Terms, 2023). Pharmacological adherence, identified as the primary determinant of treatment success, involves aligning a person's behavior with the health professional's recommendations, integrating the doctor's instructions with the patient's lifestyle, beliefs, and preferences, according to the World Health Organization (WHO) (Jimmy & Jose, 2011a). Factors influencing adherence, categorized into patient-related, disease-related, treatment-related, health system-related, medical team-related, and socio-economic factors, will be evaluated in this study (Padilha et al., 2021).

Despite a 50% adherence rate in developed countries reported by the WHO, patients with chronic diseases show a wide range of adherence rates, from 6-67% (Jimmy & Jose, 2011b; Unni E & Farris KB, n.d.). The variance observed, highlighted by a McKinsey study showing that between 26% and 63% of patients with chronic diseases do not adhere to their prescribed treatment regimen, underlines the need to explore new therapies while recognizing that a new therapy alone may not solve the problem of non-adherence. Improved tolerability of drugs, coupled with better adherence, is crucial to reduce the need for medication switching (Jason Hichborn et al., 2018). Non-adherence impacts treatment efficacy and contributes to increased patient burden, a measure of a health condition's impact on daily activities influenced by morbidity (Poitras et al., 2012). Efficient pharmacological adherence is posited as a significant mitigating factor, potentially leading to substantial annual savings in medical costs of as much as $269 billion in avoidable medical costs, representing approximately 4.6% of total health expenditures (Kasahun et al., 2022).

Previous studies have shown that the combined measurement of burden and morbidity is a more accurate predictor of patient-related outcomes than a simple disease count. This combination is essential as it provides a complete picture of the impact of diseases on patients' lives. Furthermore, understanding disease burden is a tool for tailoring effective healthcare strategies to address patients' specific needs and improve their quality of life. It is essential to allocate resources and plan appropriate interventions to manage chronic conditions optimally, thereby improving adherence to treatment (Büyüm AM et al., n.d.; Poitras et al., 2012). This confirms why the three dimensions' interaction is the study's key.

A-CaMo II arises from a knowledge gap on adherence, burden, and morbidity in patients with chronic diseases in the Dominican Republic. Building on the insights gained from A-CaMo I, a cross-sectional research study conducted in a primary care setting in Santo Domingo, the study utilizes tools like the Medication Adherence Reasons Scale (MAR-Scale) and the Disease Burden Morbidity Assessment (DBMA). The first phase, A-CaMo I, prompted the need for a second phase due to the limitations of the social context. A-CaMo II, conducted in a different social environment, addresses the clinical question: "In patients over 18 years with chronic diseases attending the Centro Médico de Diabetes, Obesidad y Especialidades (CEMDOE) in Santo Domingo in August 2023, what is the pharmacological adherence, burden, and morbidity?" The primary endpoint measures patients' adherence, burden, and morbidity to their pharmacological habits and diseases. In contrast, secondary endpoints include determining reasons for medication non-adherence, assessing the impact of diseases on daily activities, and establishing a correlation between burden and non-adherence through an ordinal regression model.

Design

The cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies published in 2023 (STROBE, 2023). Data were collected through patient interviews, and statistical analyses were performed to establish relationships between variables.

Research Site

The study's patients were screened and selected at CEMDOE, a tertiary-level healthcare center in Santo Domingo, Dominican Republic. Data collection occurred during August 2023.

Population, Sample Size, and Sampling

The study population consisted of individuals aged 18 or over who attended CEMDOE in Santo Domingo, Dominican Republic, during August 2023. Because the healthcare center could not determine the exact number of patients attending, participants were selected using a non-probabilistic convenience sampling method. Therefore, the sample size determination followed an infinite population approach. Sample size computation considered the following specific parameters: a Z score of 1.96, with a 95% confidence level, a 5% alpha (type 1 error), a 20% beta (type II error) corresponding to an 80% statistical power, and an expected proportion of 50% (Brown et al.; J. K., 2011). These parameters led to a

required sample size of 384 patients.

Inclusion and Exclusion Criteria

The inclusion criteria for sample selection consisted of the following: 1) patients aged 18 years or older; 2) individuals diagnosed with at least one chronic disease in the MAR-Scale or DBMA; 3) patients who attend CEMDOE for consultation. The exclusion criteria were: 1) patients who have a chronic disease present in the MAR-Scale but are not currently receiving pharmacological treatment for said disease; 2) individuals who are not proficient in either English or Spanish; 3) patients with physical or cognitive limitations that obstruct effective communication.

Data Collection and Procedures

The patients were evaluated for potential inclusion during the waiting period preceding their doctor's appointment. Selected patients underwent oral interviews, where two questionnaires and a scale were administered. Before participating, individuals provided informed consent (Appendix #1). The document outlined the study's subject, objectives, tools, and data reliability.

Data collection was conducted on weekdays, with two sessions per day, one in the morning from 9 a.m. to 1 p.m. and one in the afternoon from 2 p.m. to 6 p.m., from August 7th to 28th, 2023. To ensure effective patient interaction, the research team received training from medical students in their third, fourth, or fifth year of studies who had been instructed in clinical/surgical semiology.

Sociodemographic Questionnaire and Variables

To gather patients' sociodemographic characteristics, the authors of the study developed a questionnaire (Appendix #2) based on two preceding forms from the CDC and WHO (National Center for Chronic Disease Prevention and Health Promotion, 2022; Üstün et al., 2015), adapted to a local context (i.e., income in Dominican Pesos)—the questionnaire considered binary nominal qualitative variables such as sex and the presence of past medical history. Multiple nominal qualitative variables were utilized for a more comprehensive picture, encompassing gender identity, residence, ethnic background, marital status, religious affiliation, occupation, and the patient's medical insurance status.

In addition, the patients' level of education was assessed as a multiple ordinal qualitative variable. Multiple ordinal qualitative variables, which encompassed economic income, age, duration of the disease, and the length of time the patient had been using the prescribed medication, further provided insights into the patients' backgrounds.

MAR-Scale: Tool interpretation

Pharmacological adherence was assessed using the MAR-Scale (Unni et al., 2019). It involved a structured approach wherein patients were initially categorized based on chronic disease. Further classification included determining the time of diagnosis, whether within the last five years or more than five years ago and the precise time since the initial prescription of the medication. Additionally, the method of drug administration was identified and categorized into injectable, oral, or topical.

The MAR-Scale comprises four distinct components, each aimed to evaluate medication adherence over specific time intervals. These components include an assessment of reasons for non-adherence during the preceding seven days, a count of the number of days with medication adherence within the same 7-day timeframe, an assessment of reasons for non-adherence over the past four weeks, and a count of the number of weeks with adherence within the last four weeks.

Based on the data collected through these components, the MAR-Scale quantifies adherence according to 4 defined criteria: the Adherence by Reasons Score for the last seven days, ranging from 0 to 133, with a threshold of 30 to categorize a patient as adherent; the Adherence by Quantity Score for the last seven days, ranging from 0 to 7, where scores of 0-2 indicate adherence and 3-7 indicate non-adherence; the Adherence by Reasons Score for the last four weeks, ranging from 0 to 76, with a maximum adherence score of 20; and finally, the Adherence by Quantity Score for the last four weeks, ranging from 0 to 4, where scores of 0-1 denote adherence and 2-4 signify non-adherence. The present study's authors set these bright lines for adherence vs. non-adherence.

DBMA: Tool Interpretation

In addition to the MAR-Scale, the study also incorporated the DBMA (Appendix #3). The DBMA aims to assess the overall impact of chronic disease across two dimensions: burden and morbidity. First, the burden is measured using a Likert scale with five categories ranging from "Not at all" to "A lot," with assigned values from 1 to 5, respectively, to measure the impact of the disease on the patient's daily life.

Second, morbidity is assessed by considering the number of diseases a single patient has, classifying

patients with only one disease as "monomorbid" and those with multiple diseases as "multimorbid" (Poitras et al., 2012).

Diseases Present in the MAR-Scale and the DBMA.

The MAR-Scale includes 17 chronic diseases: atopic dermatitis, chronic pain, chronic constipation, depression, diabetes mellitus, epilepsy, gastroesophageal reflux, inflammatory bowel disease, irritable bowel syndrome, migraine-type headache, multiple sclerosis, systemic lupus erythematosus, osteoporosis, psoriasis, overactive bladder, rheumatoid arthritis, and sleep disorders (Unni et al., 2019).

The DBMA covers 22 chronic diseases: asthma, back pain or sciatica, cancer, cerebrovascular events, cholesterol problems, depression or anxiety issues, diabetes, heart disease, heart failure, hearing problems, hypertension, intestinal issues, leg circulation issues, lung problems (chronic bronchitis or emphysema), osteoarthritis, osteoporosis, other diseases affecting the limbs or joints for more than six months (such as tendinitis, bursitis, fibromyalgia, lupus, etc.), overweight, reflux or acidity or peptic ulcer, rheumatoid arthritis, thyroid disorders, and vision problems (Bayliss et al., 2005; Wijers et al., 2019).

To account for other diseases, the DBMA also incorporates a final question: "Do you suffer from ANOTHER or MANY OTHER chronic health issues that were not mentioned above?"—allowing for the assessment of the burden of additional chronic conditions that may not be part of the questionnaire's predefined list of chronic diseases.

Both of the scales share four common diseases: depression, diabetes mellitus, rheumatoid arthritis, and osteoporosis, which served as the common ground for the regression analysis performed.

Statistics

A thorough analysis was conducted, considering both quantitative and qualitative data. All the descriptive and inferential analyses were carried out using Microsoft Excel 365, 2021, and STATA BE version 18, 2023. Quantitative data were summarized using the arithmetic mean to measure central tendency and the standard deviation to assess data dispersion. Absolute and relative frequency were both used to condense quantitative information. These statistical approaches were chosen based on the assumption of data normality, supported by the Central Limit Theorem for an $n > 30$ ($n = 384$).

Morbidity was analyzed by determining the frequency of monomorbid and multimorbid patients within the sample, and the results were presented in a consolidated table.

A table was constructed to accomplish the first secondary endpoint. The reasons for nonadherence identified by the MAR-Scale were outlined and organized according to frequency. The table included the percentage of participants affected by each reason, emphasizing the top three most frequent ones.

The burden associated with each disease, as determined by the DBMA, was calculated for other secondary endpoints. This involved determining the mean and standard deviation for each condition and the number of patients impacted by them.

Inferential Statistics

Creating an ordinal regression analysis was the last secondary endpoint. The model sought to establish a correlation between the pharmacological adherence score and the burden experienced by patients suffering from the four common diseases: diabetes mellitus, rheumatoid arthritis, osteoporosis, and depression. The model considered the Adherence by Weekly Reason Score as the independent variable and the burden as the dependent variable. Statistical significance was defined by $p < 0.05$, and the model is reported alongside odds ratio (OR) for each burden category.

The independent variable was measured on a quantitative, continuous scale, whereas the dependent variable was measured on an ordinal, categorical one. The chronic disease suffered was included as a confounding factor to make the analysis more robust.

Bias

While preparing the research proposal, the study considered several sources of bias that were plausible but difficult to address due to the nature of the study measures and environment. The main concerns were selection bias, the Hawthorne effect, confounding factors, and observer bias. Selection bias is likely present due to the sampling methodology. Hawthorne effect and observer bias are another possibility due to how the study interviewers assessed each patient in the waiting area of the CEMDOE consult wing. Lastly, confounding factors were considered. However, due to the raw amount of factors that could lead to a confounding effect, correlation models were used to control for which chronic disease the patient was afflicted with. Patient disease status was the main confounder between pharmacological adherence and disease burden. About these adjustments, indeed, numerous other variables were not adjusted in the model. Therefore, confounding factors, neither measured nor excluded,

are present in the study.

Missing Data

A complete case analysis (CCA) was conducted. Therefore, only patients with complete forms were included.

Ethics

The study obtained approval from the Independent Review Board (IRB) of Ethics at Hospital Pediatrico Dr. Hugo Mendoza (Appendix #4). Subsequently, CEMDOE issued a letter of no objection (Appendix #5) and granted permission to use their name in the study (Appendix #6), initiating the data collection process at their facilities. Every process undertaken during the study was made to adhere to national and international bioethical guidelines, as per the Declaration of Helsinki and the safeguard of human rights in human studies.

Results

Key Results

The sociodemographic characteristics of the patients under investigation were collected and presented in Table 1. These characteristics were further categorized based on weekly adherence status and burden. Based on these data, those with a per-week reason score have a mean age of 59.71 ± 15.23, which corresponds to 144 patients. On the other hand, those with a burden greater than or equal to 5 present a mean age of 57.29 ± 14.97, representing 284 patients.

Among the noteworthy results, we observed that patients with private health insurance exhibited higher adherence, accounting for 65.97% of cases, corresponding to 95 patients. In this group, 70.07% (199 individuals) had a burden score greater than or equal to 5.

Similarly, patients with higher levels of education demonstrated greater adherence, constituting 63.89% of cases, totaling 92 patients. Interestingly, within this subgroup, 70.42% (200 individuals) had a burden score greater than or equal to 5.

It is also noteworthy that most of the patients in the study reported a high burden, with a mean total burden per patient of 10.3 ± 8.1. In addition, the study revealed that most patients had multimorbidity, with a significant 88.8% having more than one chronic disease.

Interestingly, despite being the most prevalent chronic condition, hypertension had the lowest burden, with an average impact of 1.63 ± 1.13. Hypertension affected a significant 76.76% of the population, encompassing 294 patients.

The ordinal regression analysis unveiled a significant correlation ($p = 0.001$) between nonadherence and disease burden, indicating a 0.29 ± 0.09 unit increase in burden for every one-point decrease in adherence score.

Table 1 compiles the sociodemographic characteristics of the 384 patients who participated in the research. The patients were analyzed based on their adherence and non-adherence in two dimensions: weekly ratio and weekly amount, along with their level of disease burden. The participants were categorized into various sociodemographic groups: age, sex, marital status, residence, nationality, religion, health insurance, education level, income, and past medical history.

Among these patients, those with private health insurance demonstrated a higher adherence rate, with 65.97% (95 patients) showing greater adherence. Additionally, this group had a significant portion, 70.07% (199 patients), with a disease burden level greater than or equal to 5.

Patients with higher education levels also exhibited greater adherence at a rate of 63.89% (92 patients), and a substantial 70.42% (200 patients) had a disease burden greater than or equal to 5.

Regarding economic income, patients with an income greater than RD$75,000 showed greater adherence in 40.97% of cases (59 patients), and 41.55% (118 patients) had a disease burden level greater than or equal to 5.

Table 2 shows the adherence, burden, and morbidity levels of the population that participated in the study, which consisted of 384 patients. However, it is important to consider that one of the surveyed patients' burdens was not measured, leading to a sample size of 383 for burden and morbidity assessment. The patient was not suffering any of the 22 conditions inquired for in the DBMA questionnaire, hence being only assessed through the MAR-Scale. 146 patients with MAR-Scale diseases were grouped into adherence by daily and weekly scores.

Adherence by daily ratio was observed to range from 1.9 ± 5.8, while adherence by weekly ratio ranged from 2.1 ± 7.2. The total burden per patient varies by 10.3 ± 8.1. In addition, it is highlighted that most of the patients were diagnosed with more than one disease, conditioning them as patients with multimorbidity, representing 88.77%, equivalent to 340 patients.

Table 3 reflects the most frequent reasons why the patients surveyed with the MAR-Scale, representing a total of 149 people, did not follow their pharmacological treatment. When highlighting the 3 most frequent reasons, the statement "I would have used

	Adherent, n (144), per weekly reason score	**Adherent, n (128), per weekly amount score**	**Non-adherent, n (2), per weekly reason score**	**Non-adherent, n (18), per weekly amount score**	**Burden < 5, n (99)**	**Burden ≥ 5, n (284)**
Age, mean ± SD (years)	59.71 ± 15.23	61.16 ± 14.74	76.50 ± 13.44	51.22 ± 16.74	55.43 ± 15.17	57.29 ± 14.97
Sex:						
Male, n (%)	60 (41.67%)	57 (44.53%)	0 (0%)	3 (16.67%)	60 (60.61%)	91 (32.04%)
Female, n (%)	84 (58.33%)	71 (55.47%)	2 (100%)	15 (83.33%)	39 (39.39%)	192 (67.61%)
Other, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.35%)
Gender:						
Man, n (%)	56 (38.89%)	53 (41.41%)	0 (0%)	3 (16.67%)	61 (61.62%)	95 (33.45%)
Woman, n (%)	88 (61.11%)	75 (58.59%)	2 (100%)	15 (83.33%)	38 (38.38%)	189 (66.55%)
Marital status:						
Single, n (%)	36 (25.00%)	31 (24.22%)	0 (0%)	5 (27.78%)	25 (25.25%)	58 (20.42%)
Married, n (%)	78 (54.17%)	70 (54.69%)	1 (50%)	9 (50%)	62 (62.63%)	157 (55.28%)
Divorced, n (%)	9 (6.25%)	7 (5.47%)	0 (0%)	2 (11.11%)	5 (5.05%)	17 (5.99%)
Widowed, n (%)	15 (10.42%)	15 (11.72%)	1 (50%)	1 (5.56%)	1 (1.01%)	32 (11.27%)
Domestic partnership, n (%)	6 (4.17%)	5 (3.91%)	0 (0%)	1 (5.56%)	6 (6.06%)	20 (7.04%)
Residence:						
Northern Region, n (%)	2 (1.39%)	2 (1.39%)	0 (0%)	0 (0%)	1 (1.01%)	5 (1.76%)
Southeast Region, n (%)	130 (90.28%)	115 (79.86%)	2 (100%)	16 (11.11%)	93 (93.94%)	260 (91.55%)
Southwest Region, n (%)	12 (8.33%)	10 (6.94%)	0 (0%)	2 (1.39%)	5 (5.05%)	18 (6.34%)
Other*, n (%)	1 (0.69%)	1 (0.69%)	0 (0%)	1 (0.69%)	0 (0%)	1 (0.35%)
Nationality:						
Dominican, n (%)	139 (96.53%)	123 (96.09%)	2 (100%)	18 (100%)	97 (97.98%)	272 (95.77%)
Foreign citizen, n (%)	5 (3.47%)	5 (3.91%)	0 (0%)	0 (0%)	2 (2.02%)	12 (4.23%)
Ethnicity:						
Afro-latino, n (%)	18 (12.50%)	17 (13.28%)	0 (0%)	1 (5.56%)	11 (11.11%)	25 (8.80%)
White Caucasian, n (%)	8 (5.56%)	8 (6.25%)	0 (0%)	0 (0%)	3 (3.03%)	25 (8.80%)
Hispanic Latino, n (%)	116 (80.56%)	101 (78.91%)	2 (100%)	17 (94.44%)	85 (85.86%)	233 (82.04%)
Other, n (%)	2 (1.39%)	2 (1.56%)	0 (0%)	0 (0%)	0 (0%)	1 (0.35%)
Religion:						
Christianity, n (%)	105 (72.92%)	94 (73.44%)	0 (0%)	11 (61.11%)	68 (68.69%)	217 (76.41%)
Atheism, n (%)	8 (5.56%)	8 (6.25%)	0 (0%)	0 (0%)	10 (10.10%)	14 (4.93%)
Agnosticism, n (%)	5 (3.47%)	4 (3.13%)	0 (0%)	1 (5.56%)	3 (3.03%)	8 (2.82%)
Other, n (%)	26 (18.06%)	22 (17.19%)	2 (100%)	6 (33.33%)	18 (18.18%)	45 (15.85%)
Occupation:						
Student, n (%)	1 (0.69%)	1 (0.78%)	0 (0%)	0 (0%)	2 (2.02%)	2 (0.70%)
Public/private service, n (%)	82 (56.94%)	70 (54.69%)	0 (0%)	12 (66.67%)	68 (68.69%)	175 (61.62%)
Housekeeping, n (%)	25 (17.36%)	23 (17.97%)	2 (100%)	4 (22.22%)	8 (8.08%)	59 (20.77%)
Retired, n (%)	20 (13.89%)	20 (15.63%)	0 (0%)	0 (0%)	8 (8.08%)	33 (11.62%)
Other, n (%)	16 (11.11%)	14 (10.94%)	0 (0%)	2 (11.11%)	13 (13.13%)	15 (5.28%)

Table 1: *Sociodemographic variables according to adherence, burden, and morbidity (n = 384).*

Insurance:						
Government, n (%)	45 (31.45%)	40 (31.25%)	2 (100%)	7 (38.88%)	39 (39.39%)	75 (26.41%)
Private insurance, n (%)	95 (65.97%)	85 (66.41%)	0 (0%)	10 (55.56%)	54 (54.55%)	199 (70.07%)
International insurance, n (%)	2 (1.39%)	1 (0.78%)	0 (0%)	1 (5.56%)	2 (2.02%)	3 (1.06%)
Without insurance, n (%)	1 (0.69%)	1 (0.78%)	0 (0%)	0 (0%)	1 (1.01%)	1 (0.35%)
Doesn't know, n (%)	1 (0.69%)	1 (0.78%)	0 (0%)	0 (0%)	3 (3.03%)	6 (2.11%)
Education:						
Primary school, n (%)	16 (11.11%)	15 (11.72%)	1 (50%)	2 (11.11%)	9 (9.09%)	24 (8.45%)
High school, n (%)	27 (18.75%)	22 (17.19%)	0 (0%)	5 (27.78%)	22 (22.22%)	51 (17.96%)
College, n (%)	92 (63.89%)	82 (64.06%)	1 (50%)	11 (61.11%)	66 (66.67%)	200 (70.42%)
None of the above, n (%)	9 (6.25%)	9 (7.03%)	0 (0%)	0 (0%)	2 (2.02%)	9 (3.17%)
Income:						
Less than RD$15,000, n (%)	10 (6.94%)	10 (7.81%)	1 (50%)	1 (5.56%)	5 (5.05%)	23 (8.10%)
RD$15,000-75,000, n (%)	48 (33.33%)	42 (32.81%)	0 (0%)	6 (33.33%)	33 (33.33%)	90 (31.69%)
More than RD$75,000, n (%)	59 (40.97%)	52 (40.63%)	1 (50%)	8 (44.44%)	52 (52.53%)	118 (41.55%)
No income, n (%)	27 (18.75%)	24 (18.75%)	0 (0%)	3 (16.67%)	9 (9.09%)	53 (18.66%)
Past medical history **						
Respiratory:						
Yes, n (%)	29 (20.14%)	26 (20.31%)	0 (0%)	3 (16.67%)	8 (8.08%)	65 (22.89%)
No, n (%)	115 (79.86%)	102 (79.69%)	2 (100%)	15 (83.33%)	91 (91.92%)	219 (77.11%)
Cardiovascular:						
Yes, n (%)	100 (69.44%)	95 (74.22%)	2 (100%)	7 (38.89%)	78 (78.79%)	221 (77.82%)
No, n (%)	44 (30.56%)	33 (25.78%)	0 (0%)	11 (61.11%)	21 (21.21%)	63 (22.18%)
Endocrinology:						
Yes, n (%)	8 (5.56%)	111 (86.72%)	0 (0%)	8 (44.44%)	38 (38.38%)	138 (48.59%)
No, n (%)	136 (94.44%)	17 (13.28%)	2 (100%)	10 (55.56%)	63 (63.64%)	146 (51.46%)
Surgical:						
Yes, n (%)	99 (68.75%)	89 (69.53%)	1 (50%)	11 (61.11%)	57 (57.48%)	208 (73.24%)
No, n (%)	45 (31.25%)	39 (30.47%)	1 (50%)	7 (38.89%)	42 (42.42%)	76 (26.76%)
Blood transfusions:						
Yes, n (%)	9 (6.25%)	7 (5.47%)	0 (0%)	2 (11.11%)	8 (8.08%)	27 (9.51%)
No, n (%)	135 (93.75%)	121 (94.53%)	2 (100%)	16 (88.89%)	91 (91.92%)	257 (90.49%)
Infectious diseases:						
Yes, n (%)	3 (2.08%)	3 (2.34%)	1 (50%)	1 (5.56%)	3 (3.33%)	14 (4.93%)
No, n (%)	141 (97.92%)	125 (97.66%)	1 (50%)	17 (94.44%)	96 (96.97%)	270 (95.07%)

*Patient staying in the Dominican Republic, but resides in another country

Table 1: *(Continued) Sociodemographic variables according to adherence, burden, and morbidity (n = 384).*

it, but I simply forgot" predominates, with a percentage of 16.11%, equivalent to 24 patients. Second, "I would have used it, but I forgot due to occupations or changes in their routine," representing 11.41% of the respondents, equivalent to 17 patients. Moreover, the third would be "No longer need the medication," with 10.74%, equivalent to 16 patients. Table 4 displays the breakdown, by disease, of relative frequencies of reasons for daily non-adherence. IBS, psoriasis, and migraine boast a non-adherence rate of 100% on the daily reasons scale. However, it is important to note that these three conditions had low sample sizes: one patient for the first two conditions and two for the latter. As can be corroborated by Table 3, the reasons with the highest relative frequencies for non-adherence were skipping the medicine to see if it was still needed, unavailability of refills, social reasons, medicine is not a priority, the patient does not think they need it, they forgot due to a busy schedule, or they missed it. For all diseases, at least one of these reasons was given to explain the patient's non-adherence. For psoriasis, depression, diabetes, osteoporosis, and arthritis, all three of the most frequent reasons were given.

The chronic diseases present in the MAR-Scale but not detailed in this table were excluded due to the absence of reported reasons for daily non-adherence. Due to two factors: (1) no patient in the sample reported said disease or condition; (2) all interviewed patients took their medicine in the last 7 days.

Table 5 presents the disease impact levels in the population that participated in the study, including 383 patients. Seven principal diseases are presented as the one or two most important in the study per body system. The entire table can be found as a supplement (Supplementary Table 1). The table was based on 1460 observations collected, as several patients had multiple diseases, resulting in a total sum greater than the expected 100% when accounting for all 23 chronic diseases in the entire table.

Hypertension emerges as the most predominant chronic disease, affecting 76.76% of the population, equivalent to 294 patients, with a mean impact of 1.63 ± 1.13. The chronic disease with the greatest observed burden was osteoarthritis, with 4.20 ± 1.27, yet only influencing 3.92% of the population. Following closely was cancer, with a burden of 4.17 ± 1.27, impacting 3.13% of the study population.

In Table 6, the results of the ordinal regression analysis are presented, which aimed to examine the relationship between weekly reasons score adherence as an independent quantitative and continuous variable and disease burden as a dependent categorical and ordinal variable. The latter was treated as categorical due to an initial numerical transformation. Chronic disease status was included as a confounding factor, defining the adjusted nature of the model and enhancing its statistical robustness.

A statistically significant correlation was found, with a p-value of 0.001, between nonadherence as a predictor and disease burden. Indicating that for every one-point increase in the patient's adherence score (indicating lower adherence due to a specific reason), their disease burden increased by 0.29 ± 0.09 units. Notably, less adherent patients were more likely to surpass a specific threshold, resulting in an increased disease burden, especially if they were already close to that threshold.

On the other hand, MacFarden's pseudo $R\hat{2}$ highlighted an explanation of only 0.0712. Suggesting that patient perceptions of disease burden are explained by adherence behavior to the extent of 7.12%. However, the model's odds ratio was 1.33 ± 0.12, indicating that, as adherence scores increase, disease burden tends to increase. Said findings support a positive relationship between the analyzed variables.

Discussion

Key Results

To comprehend the levels of adherence, an evaluation was conducted within a range based on two scores: one representing the last 7 days and the other reflecting the last 4 weeks. Daily adherence exhibited fluctuation, while weekly adherence displayed variability. Subsequently, comparisons with previous findings will be presented in conjunction with the specific objectives.

Direct comparison with existing literature regarding disease burden can be challenging due to inherent difficulties in quantifying its multifaceted nature. At the same time, the development of evaluative tools represents a commendable effort. Their inherent limitations must be acknowledged. Patient-reported outcomes, a cornerstone of such tools, are inevitably subjective and susceptible to individual variability. This subjective component introduces inherent challenges in achieving truly objective disease burden measurements. Consequently, a significant portion of published literature focuses on the burden of pharmacological interventions, given the relative objectivity provided by quantifiable variables associated with medication use and side effects.

The present study examined pharmacological nonadherence for 146 patients. Another study using the same scale coincided with the most frequent reason for non-adherence, "I would have used it, but I simply forgot." However, the second and third reasons varied, being "I forgot because I was too busy or due to a change in routine" and "I think I no longer

Adherence*, n (146), mean ± SD**	
Adherence by daily reasons score (0-49)	1.932 ± 5.828
Adherence by daily amount score (0-7)	0.740 ± 1.879
Adherence by weekly reasons score (0-52)	2.062 ± 7.196
Adherence by weekly amount score (0-4)	0.589 ± 1.131
Burden*, n (383), mean ± SD**	
Score per patient (1-43)	10.261 ± 8.080
Per disease*** (1-5)	2.692 ± 1.570
Morbidity, n (383), n (%)	
Monomorbid	43 (11.23%)
Multimorbid	340 (88.77%)

***Observed ranges. Possible ranges, in descending order: (0-133), (0-7), (0-76), (0-4), (0-115), (1-5); ****SD: Standard Deviation; *****based on 1460 observations obtained from 343 patients.

Table 2: *Adherence, burden, and morbidity of patients with chronic diseases (n = 384).*

Reasons for weekly non-adherence	**Patients, n (%)**
I would have used it but simply forgot about it.	24 (16.11%)
I would have used it, but I forgot because I was too busy, or because of a change in routine.	17 (11.41%)
I don't think I need the medicine anymore.	16 (10.74%)
I would have used it, but I have difficulty remembering things in my daily life.	10 (6.71%)
The medication is not a high priority in your daily routine.	10 (6.71%)
Problems managing all prescribed medications.	8 (5.37%)
I have not felt comfortable using it for personal reasons.	8 (5.37%)
I have not felt comfortable using it for social reasons.	8 (5.37%)
I didn't have the medication because the pharmacy or provider ran out of it.	7 (4.7%)
I sometimes skip using the medication to see if I still need it.	6 (4.03%)
I worry about possible side effects of the medication.	6 (4.03%)
I didn't have the medicine because I didn't have a way to get to the pharmacy or provider.	5 (3.36%)
I have had side effects from the medicine.	4 (2.68%)
I didn't have the money to pay for the medicine.	4 (2.68%)
I think the medicine is not working for me.	4 (2.68%)
Concerns about long-term effects from the medicine	4 (2.68%)
Difficulty swallowing/difficulty injecting the medicine.	3 (2.01%)
Not sure how to take the medicine.	3 (2.01%)
Difficulty opening container/getting the injection ready to use.	2 (1.34%)

Table 3: *Most frequent reasons for non-adherence (n = 149).*

Reasons for daily non-adherence	IBS	Psoriasis	Migraine	Depression	Diabetes	Osteoporosis	Arthritis
Overall rate of non-adherence	100%	100%	100%	12.50%	8.41%	66.67%	25%
Difficulty opening container/getting the injection ready to use	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	33.33%
Not sure how to take the medicine	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	33.33%
Difficulty swallowing/difficulty injecting	0.00%	0.00%	0.00%	0.00%	2.86%	0.00%	33.33%
Long term effects from the medicine	0.00%	0.00%	0.00%	0.00%	8.57%	16.67%	33.33%
Medicine is not working	0.00%	0.00%	0.00%	0.00%	8.57%	33.33%	33.33%
Cost of medicines	0.00%	0.00%	0.00%	50.00%	5.71%	0.00%	33.33%
Side effects	0.00%	0.00%	0.00%	0.00%	8.57%	33.33%	33.33%
Transportation issues	0.00%	0.00%	0.00%	0.00%	8.57%	0.00%	33.33%
Possible side effects	0.00%	0.00%	0.00%	0.00%	11.43%	16.67%	33.33%
Skip to see if it is still needed	0.00%	100.00%	0.00%	50.00%	5.71%	33.33%	33.33%
Pharmacy was out of this medicine/I ran out of refills	100.00%	0.00%	0.00%	0.00%	11.43%	16.67%	33.33%
Social reasons such as with friends	0.00%	0.00%	50.00%	0.00%	17.14%	0.00%	33.33%
Personal reasons such as overwhelmed with medicines	0.00%	0.00%	50.00%	50.00%	8.57%	16.67%	66.67%
Trouble managing all the medicines	0.00%	0.00%	0.00%	50.00%	11.43%	0.00%	33.33%
Do not consider taking this medicine as a priority	0.00%	100.00%	0.00%	100.00%	14.29%	33.33%	66.67%
Forgot due to cognitive issues	0.00%	0.00%	50.00%	0.00%	14.29%	33.33%	33.33%
Don't need this medicine anymore	0.00%	100.00%	50.00%	50.00%	28.57%	33.33%	100.00%
Forgot due to busy schedule	100.00%	100.00%	50.00%	0.00%	28.57%	33.33%	33.33%
Simply missed it	0.00%	100.00%	50.00%	0.00%	54.29%	50.00%	33.33%

Table 4: *Most frequent reasons for non-adherence according to disease (n=149).*

Chronic Disease	Number of Patients *, n (%) (n=383)	Burden, mean ± SD
Osteoarthritis	15 (3.92%)	4.20 ± 1.27
Cancer **	12 (3.13%)	4.17 ± 1.27
Rheumatoid Arthritis	28 (7.31%)	3.64 ± 1.47
Cerebrovascular Accident (CVA)	14 (3.66%)	3.64 ± 1.78
Depression or Anxiety Problems	59 (15.40%)	3.34 ± 1.18
Heart Failure	7 (1.83%)	3.29 ± 1.80
Hypertension	294 (76.76%)	1.63 ± 1.13

***** Percentage exceeds 100% due to multimorbidity; ****** In the 5 last years (including melanoma, but excluding all other skin cancers).

Table 5: *Level of burden of six diseases on the patient's daily life (n = 383).*

	Coefficient	Confidence level (95%)
Model	0.29 ± 0.09	[0.11 – 0.47]
Cut #1 (Burden 1 to 2)	0.37 ± 0.32	[-0.26 – 1.00]
Cut #2 (Burden 2 to 3)	0.83 ± 0.33	[0.19 – 1.47]
Cut #3 (Burden 3 to 4)	1.78 ± 0.36	[1.07 – 2.48]
Cut #4 (Burden 4 to 5)	2.47 ± 0.40	[1.68 – 3.25]
Pseudo		

Pseudo R2 = 0.0712; z = 3.20; OR = 1.33 ± 0.12 [1.12 – 1.59]; adjusted p-value = 0.001

Table 6: *Ordinal regression analysis between adherence and burden (n = 125).*

need the medication" in the present study, and "side effects" and "concern about long-term effects" in the reference study (Unni et al., 2019). These variations could be attributable to sociodemographic differences in the samples of both studies.

In contrast to a previous study (Padilha et al., 2021), where only 43% of patients were adherent to treatment, the present study found a significantly higher proportion of adherence at 87.67%. These disparities may be attributed to the Brazilian study's different social and economic factors. Notably, the previous study identified treatment complexity, alcohol consumption, and reliance on the public healthcare system as major reasons for non-adherence. However, in the current study conducted in a private tertiary healthcare facility (A-CaMo II), issues with treatment complexity were among the least frequently reported reasons (see Table #3).

Among chronic diseases assessed, hypertension emerged as the most prevalent but exhibited a moderate impact on patients' daily routines. Hypertension had a moderate impact on patients' daily lives. These findings suggest that hypertension is common but does not substantially disrupt daily routines. However, potential confounding factors like limited disease awareness among hypertensive patients warrant further exploration, as they might attenuate self-reported burden levels. In contrast, osteoarthritis had the most significant impact.

In a previous study (Poitras et al., 2012) conducted on the Canadian population, the most frequently reported condition among respondents was hypertension prevalence, which reached 26.2% but ranked lower in impact than rheumatoid arthritis and joint-related conditions. Interestingly, despite the French-speaking population, the most predominant chronic diseases were similar to those found in the present study: hypertension (76.76%) and cholesterol difficulties (41.78%). Moreover, a previous study highlighted how certain diseases, such as rheumatoid arthritis, back pain, angina, and hearing concerns, significantly impact daily activities, markedly limiting the quality of life (Poitras et al., 2012). However, there is some discrepancy in comparison to the current research, as the diseases with the highest impact were osteoarthritis, cancer, rheumatoid arthritis, and other joint-related conditions. Nonetheless, both studies conclude that rheumatoid arthritis is one of the chronic diseases with a substantial impact on patients.

It is also important to note that the prevalence of chronic diseases observed in the present study was much higher than in the previous study. Such a difference could be attributed to A-CaMo II's larger sample size and significantly higher mean age.

After calculating a disease-adjusted ordinal regression analysis, a positive relationship was determined, with a rise in the patient's weekly adherence score of one point corresponding to a rise of 0.29 ± 0.09 in burden. The correlation was statistically significant and corroborated by the model's OR, which determined that a patient with a higher adherence score (i.e., less adherent) is 1.33 ± 0.12 times more likely to have a greater burden than a patient with a lower adherence score. To the author's knowledge, the methods (DBMA and MAR-Scale) used in A-CaMo II cannot be directly compared to those found in the literature. However, an abstract published in 2022 (Mettler et al.,

2022) found no correlation between disease burden and medication adherence. Aside from differences in methodology, other factors that could have accounted for these contradicting results are (a) different populations, (b) different measurement scales, and (c) the French study only evaluated autoimmune diseases. This dichotomy presents value as a field of study for future researchers, highlighting the need to study different health systems worldwide and address how the particularities of different diseases might affect adherence and burden.

These findings further emphasize the need for clinicians to address pharmacological adherence and the patient's burden accordingly. Even though the study's relationship is positive, we still require more in-depth studies that look at factors that lead to higher burden and lower adherence. More complex, intricate correlation models with other variables should be implemented and subsequently applied in the clinical setting.

Infliximab and Etanercept are part of the anti-TNF drugs used in the treatment regimen for patients with RA. Previous studies found that anti-TNF drugs were associated with TB infection in patients with RA. Thus, it is crucial to study the association between infliximab and etanercept. Our review aimed to investigate the risk of TB infection in RA patients receiving infliximab compared to those receiving etanercept. Four observational studies involving 974 in the infliximab group and 1,246 in the etanercept group meet the inclusion criteria. This review showed no difference in developing TB infection in patients with RA treated with infliximab compared to etanercept.

The last two reviews and meta-analyses included studies published until 2014 (Ai et al., 2015; Minozzi et al., 2016). For instance, Minozzi et al. (2016) reviewed 71 RCTs that used any of the five anti-TNF-α inhibitors (adalimumab, golimumab, infliximab, certolizumab, or etanercept) in rheumatological disorders - specifically for the treatment of RA, psoriatic arthritis, and ankylosing spondylitis. They found a significant association between drug use and TB occurrence. Ai et al. (2015) also reviewed 50 RCTs and 13 non-RCTs using the same five drugs and concluded that the incidence rate in the infliximab group was 2.78 times higher than in the etanercept group.

Contrary to these studies, our study narrows the scope of the review by comparing the risk of TB infection, specifically in patients with RA using infliximab versus etanercept, and includes studies from 2015 to 2022. In our examination, patients in the infliximab group showed the same Relative Risk of developing TB infection as those in the etanercept group.

Funnel plot analysis was used to assess the publication bias of the studies included in this review. The results showed a moderate publication bias, considered a disadvantage of the present work. The initial search strategy designed yielded no RCTs that met the inclusion criteria for the study. Hence, only observational studies were within the scope, another limitation of this review.

The screening and prophylaxis of LTBI and treatment of active TB are in the guidelines of the American College of Rheumatology (Singh et al., 2016) and the WHO (WHO, 2021). In the last decade, several studies have demonstrated that screening strategies can decrease the risk of TB in patients treated with biologic drugs (Gómez-Reino et al., 2007; Singh et al., 2012; Solovic et al., 2010). However, the studies evaluated here showed only a slight decrease in the incidence of TB, even when screening and prophylaxis are performed with almost 100 % penetration (Chung et al., 2020; Jung et al., 2022).

The results of LTBI screening and prophylactics for the prevention of TB show the importance of their indication for all patients with RA before treatment with biological therapy. However, many years after implementation, the studies in large populations presented here indicate that these approaches may need to be revised. Indeed, the sensitivity and specificity of screening tests, resistance to therapy against TB, and new biological drugs for RA and other rheumatic diseases that pose no risk of TB must be addressed. These results are of great importance, and other studies need to be conducted mainly in countries with a high incidence of TB. In addition, due to the difference in costs of these drugs, each cost-benefit should be considered.

Limitations

Several limitations were present in the study. The main one was that the collectors needed proper training as clinicians to interview patients at the beginning of the collection process. The lack of medical training regarding patient interviews could have led to certain discrepancies in interpreting and recording patient history; however, they received training in clinical research and managing the collected data. In addition, some diseases are present in the DBMA and not in the MAR-Scale and vice versa. Despite this, the DBMA includes a question, "Do you suffer from another or many other chronic health problems that were not mentioned above?" which allows any chronic disease that is part of the MAR-Scale to be included in the DBMA. This factor was not considered an inclusion in isolation for the latter scale, achieving 383 patients. In addition, the fact that the study was conducted in a waiting room, being a public space, could have limited the openness of the participants

in sharing information, thus affecting the validity of the results.

Although the ordered logistic regression yielded a statistically significant model, when the independent cutoffs were reviewed, it stood out that the first was insignificant. The rest of the cuts were significant, but their confidence intervals were wide. That discrepancy, especially with the model being significant, could be due to a low sample size. Thus, future researchers are encouraged to work on the model, specifically adding more data points.

Conclusion

The study effectively assessed patient adherence, burden, and morbidity associated with chronic diseases, offering a comprehensive view of these critical dimensions. The analysis revealed that most participants demonstrated being adherent, a high burden, and multimorbidity. However, it is essential to acknowledge that this study has its limitations, which should be considered for future iterations of A-CaMo.

For those who were not wholly adherent, the study identified the three most common reasons for non-adherence: "I would have used it, but I simply forgot," "I would have used it, but I forgot because I was too busy or due to a change in routine," and "I think I no longer need the medication."

Additionally, the level of burden of diseases on patients' daily activities was assessed, with osteoarthritis, cancer, other joint-related diseases, rheumatoid arthritis, and cerebrovascular accidents being the conditions that had the most substantial impact. In addition, it was determined that most patients in the sample with chronic diseases were multimorbid.

Finally, an ordinal logistic regression analysis adjusted for disease yielded a positive and statistically significant relationship between adherence by weekly reasons and disease burden.

The results of our study contribute to creating a profile of these three dimensions, adherence, burden, and morbidity, in the population of the Dominican Republic, which are essential for clinical decision-making. While conducting the study, we learned that health disparities still affect the access to medication and education on the patient's diseases. This could lead to possible interactions in the measures and correlations we sought to establish. Said disparities must be studied and analyzed in later studies and projects stemming from the A-CaMo study line. In addition, the present study's findings can be used by medical personnel in the Dominican Republic and other similar countries to provide them with information on pharmacological adherence trends in the Latino population. The A-CaMo II project is the stepping stone for more studies to uncover and approach the scientific community to understand better how better adherence leads to less disease burden and the development of multimorbidity.

Abbreviations

(A-CaMo): Adherence, Burden, and Morbidity, per its acronym in Spanish (Adherencia, Carga y Morbilidad)
(CCA): Complete Case Analysis
(CDC): Center for Disease Control and Prevention
(CEMDOE): Centro Médico de Diabetes, Obesidad y Especialidades
(DBMA): Disease Burden Morbidity Assessment
(HPV): Human Papillomavirus
(IRB): Independent Review Board of Ethics
(MAR-Scale): Medication Adherence Reasons Scale
(NCD): Non-Communicable Diseases
(NCI): National Cancer Institute
(POT): Patient-Outcome-Time
(RD): Dominican Peso (currency)
(SD): Standard Deviation
(STROBE): Strengthening the Reporting of Observational Studies in Epidemiology
(WHO): World Health Organization

Supplementary materials

Appendix 1: Informed consent;
Appendix 2: Sociodemographic Questionnaire;
Appendix 3: DMBA Questionnaire;
Appendix 4: Ethics approval letter;
Appendix 5: CEMDOE Letter of Non-Objection;
Appendix 6: Permission to use CEMDOE's name;
Supplementary Table 1: Sociodemographic variables according to adherence, burden, and morbidity (n = 384);
Supplementary Table 2: Level of impact of the diseases on the patient's daily life (n = 383).

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Conflicts of Interest

The authors declare no conflict of interest.

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