

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

HOSPITAL DE CLÍNICAS DE PORTO ALEGRE

RESIDENCIA MÉDICA EM REUMATOLOGIA

**CHALLENGES IN THE MANAGEMENT OF PSORIATIC ARTHRITIS IN LATIN  
AMERICA: A SYSTEMATIC REVIEW**

**DESAFIOS NO TRATAMENTO DA ARTRITE PSORIÁSICA NA AMÉRICA  
LATINA: UMA REVISAO SISTEMÁTICA**

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## RESUMO

A artrite psoriásica (APs) é uma doença heterogênea e de alta prevalência na América Latina (AL), acometendo cerca de 20% dos pacientes com psoríase, a qual, por sua vez, ocorrem em 0,5 a 3% da população latino-americana. Além de ser uma doença heterogênea que acomete múltiplos órgãos, estudos recentes demonstraram que a APs, frequentemente, manifesta-se de forma diferente na AL quando comparado com pacientes de outras regiões do mundo, como dos Estados Unidos e da União Europeia. Por fim, os países latino-americanos enfrentam diversas dificuldades logísticas e financeiras, as quais dificultam a implementação dos guidelines na vida real.

Em 2020, a Liga Internacional de Associações de Reumatologia (ILAR) tentou adaptar as recomendações mais recentes dos guidelines europeus e americanos para regiões mais carentes. Naquela época, a escassez de estudos clínicos examinando o manejo da APs na América Latina (AL) e em outras regiões com poucos recursos foi enfatizada pelo grupo de trabalho internacional. Em vista disso, buscou-se realizar uma revisão sistemática, com foco em estudar os principais desafios no manejo da APs na AL, tentando melhor entender as dificuldades vistas pelos médicos e pelos pacientes no acesso à saúde dos pacientes com artrite psoriásica.

A presente revisão sistemática identificou diversos fatores citados na literatura ao longo dos últimos anos, como a alta incidência de infecções oportunistas, a não adesão à terapia, a discordância entre pacientes e médicos quanto às taxas de remissão, o acesso limitado a DMARDs, as questões relacionadas à dispensação e armazenamento de medicamentos biológicos, o acesso limitado a cuidados médicos e o atraso no diagnóstico. Tais resultados enfatizaram que o manejo da APs na AL vai além do cuidado com as infecções oportunistas, mas abrange também diversas questões educacionais, culturais e logísticas. Portanto, esta revisão apresenta um forte argumento para os pesquisadores estudarem, também, essas questões logísticas, além de servir como ponto de partida para futuros projetos de pesquisa.

## **INTRODUÇÃO**

A revisão sistemática presente foi realizada em conforme com as diretrizes para a elaboração dos trabalhos de conclusão da residência médica, as quais incluem, dentre as opções de trabalho de conclusão, a realização de uma revisão sistemática.

Ainda, de acordo com as diretrizes mencionadas anteriormente, seguindo a “situação especial 3”, em concordância com o supervisor do programa de residência, submete-se o seguinte artigo como o produto final do curso de residência.

## **Desafio no manejo da artrite psoriásica na América Latina: uma revisão sistemática.**

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**Introdução.** Em 2020, a International League of Associations for Rheumatology (ILAR) publicou suas recomendações de tratamento da artrite psoriásica (APs), a qual buscou adaptar os guidelines vigentes para áreas com poucos recursos. Na época, a paucidade de literatura sobre o manejo de APs na América Latina (AL) foi ressaltada e, por isto, decidiu-se realizar uma revisão sistemática sobre o assunto.

**Métodos.** Revisão sistemática de estudos reportando, pelo menos, uma dificuldade/desafio no tratamento da APs na AL. Referências publicadas no PubMed, Embase e LILACS, entre 1980 e 2020, foram incluídas. A seleção das referências foi realizada de forma independente por dois pesquisadores no programa Rayyan QCRI. Os dados foram extraídos, independentemente, por dois outros revisores. Todos os desafios foram anotados e categorizados em domínios. A análise dos dados foi descritiva. O estudo foi registrado no PROSPERO (ID CRD42021228297).

**Resultados.** A estratégia de busca resultou em 1505 referências. Quinze estudos (13.859 pacientes) foram incluídos na análise final: a maioria foi realizada no Brasil (86,6%, N=13), recrutou pacientes em terapia biológica (80%, N=12) e eram estudos observacionais (100%, N= 15). As dificuldades enfrentadas por pacientes com APs e médicos foram a alta incidência de infecções oportunistas (descritas em 46,6% das publicações, N=7), não adesão à terapia (20%, N=3), discordância entre pacientes e médicos quanto às taxas de remissão ( 13,3%, N=2), baixa persistência de medicamentos (13,3%, N=2), acesso limitado a DMARDs (13,3%, N=2), problemas relacionados ao armazenamento de medicamentos biológicos (13,3%, N=2), custo elevado de medicamentos biológicos (13,3%, N=2), acesso limitado a cuidados médicos (6,6%, N=1) e atraso no diagnóstico (6,6%, N=1).

**Conclusão.** Os desafios no manejo da APs na AL vão além do cuidado com infecções oportunistas, mas também abrangem diversas questões educacionais e logísticas. Mais pesquisas são necessárias para entender melhor as peculiaridades do tratamento da APs na AL e, assim, melhorar o atendimento ao paciente.

## Introduction.

Psoriasis affects, on average, 1·1% of the Latin American population, with the prevalence ranging from 0·36% to 2·96% in recent studies.<sup>1</sup> Psoriatic arthritis (PsA), which occurs in 19·5% (95% CI, 17·1%-22·1%) of the South American patients with psoriasis,<sup>2</sup> is a heterogenous spondyloarthritis that may affect multiple systems and thus require a multidisciplinary care team.<sup>3</sup> In despite of its high prevalence, PsA is still scarcely studied in Latin America (LA).

In recent studies, It has been shown that PsA frequently presents differently in LA than in other regions of the United States (US) and of the European Union, with a higher prevalence of peripheral arthritis, enthesitis, and dactylitis, and a lower prevalence of extra-articular manifestations.<sup>4</sup> In addition, it was already demonstrated that even among Latin American countries there are several differences in prevalence, manifestations, and comorbidities of spondyloarthritis (SpA) patients.<sup>5</sup> Moreover, in other SpA such as ankylosing spondylitis (AS), Latin American patients had a significantly higher use of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, methotrexate (MTX), sulfasalazine (SSZ), and methotrexate-tumor necrosis inhibitor (MTX-TNFi) combination therapy than European counterparts.<sup>4</sup> Finally, Latin American countries face several difficulties commonly seen in resource-poor countries, such as logistical issues of medication distribution, endemic infections, and shortage of rheumatologists.<sup>6</sup> The shortage of rheumatologists is further complicated by the maldistribution of professionals, often with higher concentration in metropolises and scarcity in rural sectors and small cities.<sup>6</sup>

In the last two decades, there is growing interest in better understanding the peculiarities of treating PsA patients in poor-resource regions, with many organizations, such as the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), the Panamerican League of Associations for Rheumatology (PANLAR), and the International League of Associations for Rheumatology (ILAR) gathering to discuss how to better face these challenges of treatment.<sup>7</sup> The ILAR, for instance, recently funded a project to adapt for resource-deprived countries evidence-based recommendations made by the European Alliance

of Associations for Rheumatology (EULAR) and GRAPPA.<sup>8</sup> However, ILAR recommendations were limited by the paucity of literature that addressed practical questions about the management of PsA in resource-poor countries.

Therefore, it is of utmost importance to better understand the several facets of treating PsA in LA. The present work aims to identify all available literature through a systematic literature review of the challenges in the management of PsA in LA. After mapping all available data and identifying challenges in treatment, it will be possible to design studies to address the existing gaps of knowledge and then to compose public strategies targeting these challenges of treatment.

### **Methods.**

This systematic literature review was registered at PROSPERO (ID CRD42021228297) and it was conducted following PRISMA statements.<sup>9</sup> The systematic search performed on 14<sup>th</sup> of January of 2021 included references published in English, Spanish, French, and Portuguese in three databases: PubMed, Embase, and LILACS. In summary, publications were identified through a search that included all Latin American countries and the following terms: "Arthritis, Psoriatic"[Mesh] OR "Psoriatic Arthritis" OR "Arthritic Psoriasis" OR "Psoriasis Arthropathica" OR "Psoriatic Arthropathy" OR "Psoriatic Arthropathies" OR "Psoriasic Arthritis" OR "Psoriasic Arthropathy" OR "Psoriasic Arthropathies". All countries and search terms were also explored in the local languages to broaden the results.

Inclusion criteria encompassed randomized trials or observational studies published between 1980 and 2020 reporting at least one challenge faced by rheumatologists and/or PsA patients during management of disease in LA. The authors considered as challenges any obstacle and/or adversity that occurred meanwhile treating patients with PsA in LA (e.g., long delay times to start treatment, poor comprehension about the disease, non-adherence, etc.). Exclusion criteria were: review articles and abstracts without available full text.

Articles were selected through a hierarchical screening process based initially on title, then on abstract and finally on the full-text review. The selection of references was conducted independently by two authors (PEP and NSS) in the Rayyan QCRI program. Disagreements were solved by consensus. Data were then independently extracted by two reviewers (ALR and LMD), with all discordances settled by consensus.

Demographic data and main characteristics from the studies were collected and categorized according to predefined categories, such as year of publication, funding sources, study design, country, number of patients, and treatment under evaluation (conventional DMARDS – cDMARDS – and/or biological DMARDS – bDMARDS). The challenges encountered during data gathering were grouped in categories of similarity after consensus was achieved by the two authors extracting the data: opportunistic infections, non-adherence to therapy, issues related to the storage of biological drugs, discordance between patient and physician regarding remission, limited access to treatment, and other outcomes.

Bias assessment was performed following the Cochrane guidelines.<sup>11</sup> The quality of the publications was determined by establishing the initial level of certainty according to study design and further lowering or raising it according to bias assessment, where a low score reflects high quality.<sup>11,12</sup>

Analysis was mainly descriptive, with challenges described as number and frequencies of references describing that challenge among the analyzed articles. There was no funding source for this study.

## **Results.**

The search retrieved 1505 references: 1046 in Embase, 148 in LILACS, and 311 in PubMed. After the exclusion of duplicates (N=350), 1155 abstracts were analyzed for relevance, with 15 articles included in the final analysis. The flowchart representing the selection of articles is shown in Figure 1. The 15 articles included in the final analysis recruited 13,859 patients; most studies were performed in Brazil



(86.6%, N=13), and recruited patients on biological therapy (80%, N=12). All articles included in the final analysis reported observational trials (100%, N=15) with 60% of them (N=9) receiving a quality score of 4 (very low quality) and 40% (N=6) receiving a score of 3 (low quality).

The challenges on the management of PsA reported in the 15 references were: the high risk of opportunistic infections in patients using biological medication in an endemic area (46.6%, N=7), non-adherence to therapy (20%, N=3), discordance between patients and physicians regarding remission rates (13.3%, N=2), low drug persistence (13.3%, N=2), limited access to either cDMARDs or bDMARDs (13.3%, N=2), issues related to the storage of bDMARDs (13.3%, N=2), elevated cost of bDMARDs (13.3%, N=2), limited access to medical care (6.6%, N=1), and diagnostic delay (6.6%, N=1). Most studies described only one challenge (73.3%, N=11). One study described two challenges,<sup>27</sup> two studies described three challenges,<sup>22,26</sup> and one study described four challenges.<sup>24</sup>

### **Opportunistic Infections**

Seven references (46.6%) addressed the risk of opportunistic infections in spondyloarthritis (SpA) patients using bDMARDs; all these articles evaluated patients receiving TNFi.<sup>13–19</sup> The most reported opportunistic infections were active tuberculosis (TB) and latent tuberculosis infection (LTBI). LTBI prevalence in PsA patients ranged from 17.3% to 35.7%.<sup>13,17</sup> A positive tuberculin skin test (TST) reaction was less prevalent in PsA patients when compared to ankylosing spondylitis (AS) patients (30% vs 42%),<sup>13</sup> with similar results seen in other two studies.<sup>13, 17</sup> TB incidence in patients using TNFi therapy ranged from 3.8% to 6.8%,<sup>13,14</sup> with the infection usually occurring between 12 and 24 months of TNFi therapy. A single study reported four leishmaniasis cases among patients undergoing TNF therapy in Brazil (two in PsA, one in AS, and one in rheumatoid arthritis - RA - patients), in addition to reviewing twenty-eight reported cases in the literature worldwide, and demonstrated a 15 times higher risk for more severe visceral infection when compared to people not using TNFi therapy.<sup>19</sup>

### **Non-adherence to therapy**

Patient non-adherence was reported in three articles (N=3, 20%). Two Brazilian studies revealed a non-adherence rate ranging from 17.8% to 28.4%,<sup>23,24</sup> while a Latin American survey (Mexico, Colombia, and Argentina) displayed a non-adherence rate of 14.6%.<sup>25</sup> The first Brazilian study assessed adherence of PsA, RA, and AS patients to adalimumab and etanercept by assessing pharmacy dispensing records and showed a higher non-adherence rate for etanercept (38%) vs adalimumab (29.6%) and for RA (37.2%) and AS (28.4%) vs PsA (21.4%).<sup>23</sup> The second Brazilian study assessed minimal disease activity (MDA), therapy escalation and factors influencing MDA achievement by medical record review. They found that poor adherence (17.8%) and difficulty to access DMARDs (17.8%), either cDMARDs or bDMARDs, were equally important factors leading to failure to achieve MDA.<sup>24</sup>

### **Issues related to the storage of biological drugs**

Two studies, one Brazilian and one Argentinian, approached the subject of transportation and storage of thermolabile drugs (i.e., bDMARDs).<sup>20,21</sup> The first one was a prospective observational study that assessed temperature fluctuation in the refrigerator of the participants' home by collecting data continuously through 3 consecutive days.<sup>20</sup> It revealed 82.7% of the refrigerators recording temperatures outside the ideal range (between 2 °C and 8 °C) with 64.2% of all readings being above 8 °C. The authors also perceived a high risk for temperature fluctuation if the bDMARD was stored close to the freezer or on the refrigerators' door.

The second study was a cross-sectional study conducted in Argentina where 83 participants were interviewed: 77% had their bDMARD dispensed from pharmacy more than 7 days before the administration and 20% of them were not well trained regarding adequate transportation and storage.<sup>21</sup> In addition, 28% of the patients misplaced the drug at the refrigerator, with 65% of them placing it in the freezer (90% of the patients did not know the adequate temperature range at which to keep the biologic drug). Furthermore, 53% of the patients experienced power outages.

### **Discordance between patient and physician regarding remission**

Physician-patient alignment was assessed in two studies (N=2, 13.3%).<sup>24,25</sup> The first study found that the physicians had the clinical impression of PsA remission, assessed by the minimal disease activity (MDA) criteria, in spite of a non-MDA result, in 57.7% of the cases. The reason for physician clinical impression of PsA remission in spite of a non-MDA result was usually the achievement of the objective components of the MDA criteria such as swollen joints count  $\leq 1$  (in 92.3%) and PASI/BSA  $\leq 1$  (in 84.6%) and non-achievement of the subjective components such as global and pain visual analogue scales.<sup>24</sup>

The second study was a cross-sectional survey conducted across Argentina, Mexico, and Colombia to assess physician-patient alignment in PsA and reported agreement in 82.1% of pairs. Misalignment occurred significantly more in patients with moderate to severe PsA (62.5% vs 14.3%), subjective clinical impression of deteriorating disease (35.7% vs 4.3%), severe cutaneous disease (78.1% vs 48.3%), in patients with poor adherence (70% vs 88.9%), and in patients with active PsA (70.1% vs 28.1%).<sup>25</sup>

### **Limited access to treatment**

Three studies focused on limited healthcare access. In one trial, the limited access to cDMARDs and/or bDMARDs, reported by 17.8% of the patients, was the third leading cause for non-achievement of the MDA criteria.<sup>24</sup> A cross-sectional study carried out in Brazil performed a retrospective analysis of 218 administrative processes that requested cDMARDs and/or bDMARDs and found a mean time for drug dispensation of 75.2 days, with no differences between cDMARDs and bDMARDs.<sup>26</sup> Another Brazilian survey conducted in 2018 showed that approximately 60% of the patients had taken more than a year to visit a rheumatologist and about 50% received the PsA diagnosis after at least one year of the first symptoms.<sup>22</sup>

### **Other outcomes**

Drug persistence was assessed in two studies (13.3%). The first study found that a 15-day delay to initiate treatment (either cDMARDs or bDMARDs) was associated with lower drug survival, with the authors finding an overall 54.5% persistence rate at one year.<sup>26</sup> In another cohort of patients receiving TNFi, these drugs had a low retention rate: the overall persistence rate was 56.5% at month 12, with lower rates for infliximab (45.3%) compared to etanercept (56.8%) and to adalimumab (59.3%).<sup>27</sup> After 2 years of follow-up, persistence rates decreased with all drugs: infliximab (24.4%), etanercept (38.9%), and adalimumab (40.4%). In addition, lower persistence rates occurred in patients with higher Charlson comorbidity index and regions with higher proportion of low-income and low educational level. In this survey, TNFi therapy accounted for approximately 90% of all treatment costs, with costs increasing in patients with non-adherence to treatment (patients with lower medication persistence tended to require more resources from outpatient and hospital procedures).

### **Discussion.**

The present systematic review revealed important features: it demonstrated that challenges in the management of PsA in LA goes beyond the care with opportunistic infections, but also comprise several educational and logistical limitations. Besides that, it highlighted the scarcity of data about the subject in recent literature and the low quality of the available studies.

The high prevalence of opportunistic infections, mainly tuberculosis (TB), was the main challenge reported on recent publications. TB remains a major public health problem worldwide and, according to the World Health Organization (WHO), there were 10 million new TB cases and 1.4 million deaths due to TB infection in 2019.<sup>28</sup> Most Latin American countries still have an intermediate burden of TB cases, with a prevalence of LTBI around 19-20%, which is still three-to-four times higher than the prevalence of 3-5% seen in low-TB burden countries like the US.<sup>29</sup>

LTBI prevalence in PsA patients undergoing TNFi therapy in Latin America was reported in five studies, with rates ranging from 17.3% up to 35.7%, a prevalence

much higher than that seen in the US (4.4%) and in Europe (11.8%).<sup>29,30</sup> These numbers highlight the importance of TB screening previously to starting bDMARDs. In addition, these reports showed that TB infection occurred usually after 15 months of TNFi therapy, representing re-infection rather than reactivation of latent disease. This data brings into question the fact that most national recommendations among Latin American countries do not suggest annual LTBI re-screening,<sup>31</sup> contrasting with the American College of Rheumatologists (ACR) guideline which recommends annual LTBI re-screening for patients receiving cDMARDs and/or bDMARDs and living in high-risk regions.<sup>32</sup> In addition to the screening and treatment of LTBI before bDMARD therapy, the annual LTBI re-screening including chest X-ray, PPD or QuantiFERON, and medical history inquiring about new contact with TB should be considered in PsA patients living in these endemic areas.

In addition to opportunistic infections, educational issues were among the most cited challenges. The studies focused on transportation and storage of bDMARDs found alarming results: the majority of patients do not know the adequate method for medication storage and temperature recordings in most refrigerators were out of the ideal range. Frequent temperature fluctuation can lead to protein aggregates formation, which can increase immunogenicity of biologic agents and thus enhance the probability of side effects, in addition to possibly decreasing drug efficacy.<sup>33,34</sup> Simple measures such as avoiding putting the medication close to the freezer or on the door could improve medication storage. Creating folders that explain how to storage the medications is an accessible and cheap way to improve storing quality. Ideally, however, the government could implement dispensation centers for medication application instead of giving the medication and having to rely on the patients to store it.

Patient non-adherence was similar in all available studies, ranging from 14.6% to 28.4%, as well as in another Brazilian study that was published after the systematic review search was over. This latter research showed an adherence rate of 74.6% and a persistence rate of 72.1% to TNFi therapy over 1 year.<sup>35</sup> These numbers are significantly higher than the ones recently showed by the two other Brazilian studies<sup>26,27</sup> and by a data registry review performed in the US,<sup>36</sup> but similar to the ones

showed by an Italian cohort.<sup>37</sup> The US cohort had an adherence rate of 40-4%, while the Italian one displayed an adherence rate of 83-84% and a persistence rate of 53-58% in 12 months. In addition to patient adherence, physician-patient satisfaction (PPS) and alignment were also assessed, with satisfaction occurring in 80-4% of patients and PPS occurring in 82-1% of the pairs.<sup>25</sup> These rates are higher than the ones seen in surveys conducted in the US, which showed a satisfaction rate of 54-5% and an alignment rate of 76-4%.<sup>38,39</sup> These differences might reflect the importance of social norms and cultural differences of each country, as well as the importance of reinterring medication adherence as a daily habit in each patient visit. Governmental programs could be implemented, such as patient-support programs with nursing aid to increase educational levels, since it has been shown that these programs lead to increased adherence that ultimately caused decreased health-care costs.<sup>40,41</sup> Finally, as recently emphasized by EULAR, there are many possible barriers to adherence, which should be preemptively identified and overcome, being this an active, constantly evolving, blame-free process.<sup>42</sup>

Two other surveys assessed delay of treatment, drug persistence and costs of treatment. These studies found a mean delay time of 75-2 days in Brazil, which is almost a month more than the mean time of 43-9 days found in the US.<sup>43</sup> This treatment delay is especially problematic because it was associated with lower drug persistence in 12 months and because there is plenty of evidence showing that treatment delay leads to radiographic progressions and to a lower chance of sustained remission without drug.<sup>44,45</sup> Drug persistence was also inversely associated with higher Charlson comorbidity index, higher proportion of poverty, and with low educational level. Finally, it was also found that TNFi therapy was associated with 90% of all treatment costs and that patients with lower medication persistence tended to require more resources from outpatient and hospital procedures.<sup>26</sup> This annual drug cost was similar to those described in the UK and higher than the ones seen in the US in surveys conducted in the same period.<sup>46,47</sup> Therefore, creating health policies that focus on an early diagnosis (e.g., training of dermatologists and primary care physicians), fast beginning of treatment, and increased rates of drug adherence may all improve treatment quality while decreasing treatment costs, which is ultimately necessary for the preservation of the quality of care in a scenario surrounded by steeping medical costs.

There are several limitations to our study. First, most of the articles are from a single country (Brazil), which probably does not reflect the reality of all Latin American countries as there are large economic and cultural differences between these countries and most biologic drugs are available through the universal public health system in Brazil. However, in an attempt to avoid selection bias, we included in the search strategy the name of all countries in LA using the four most common languages spoken in these countries. Second, most articles included patients with both PsA, RA, and AS, with the latter two having similar challenges of treatment, but not identical ones. Whenever possible, we extracted data exclusively regarding PsA patients, but this was not possible in most articles. Finally, most articles came from university hospitals that are reference centers, which usually do not represent the reality of smaller centers and of private clinics. Full texts of abstracts and of congress texts from smaller centers were asked for but were usually unavailable and were thus excluded from the final analysis.

In conclusion, difficulties in the management of PsA in LA described in recent publication comprise the care with opportunistic infections, educational challenges, and logistical limitations. Besides the recent growing interest on the management of PsA outside Europe and North America, there is still a paucity of data on the subject and most studies were conducted solely in university hospitals. A survey with rheumatologists working in different settings such as small centers, public and private clinics, should be pursued to assess if the challenges identified in the present work truly represent the reality of different practices and countries.

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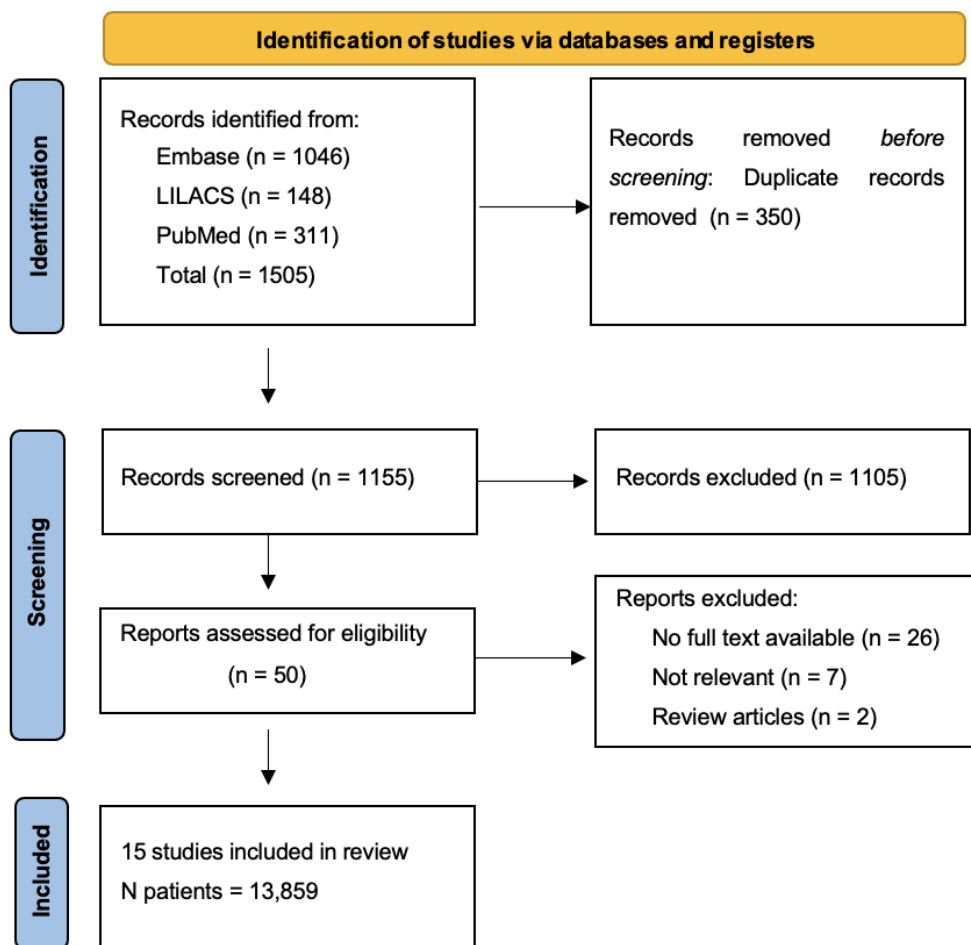
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## Figures & Tables



**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram demonstrating the selection of articles.