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Research Trends in Rare Diseases in Real-World Settings: A Scoping Review of the Last Decade (2013-2023)

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Background

- Rare diseases, also called orphan diseases, are conditions that affect a considerably less number of individuals.
- Rare diseases are associated with many challenges, including inadequate knowledge about the natural history and epidemiology, optimal diagnostic and treatment approach, management guidelines, prognostication, and treatment outcomes.
- Since rare diseases affect fewer individuals, there is little incentive for the development of drugs for these conditions compared to more prevalent health conditions. As a result, patients suffering from rare diseases often face a dual challenge of inadequate knowledge of the condition as well as limited treatment options and a lack of access to appropriate care.[1]
- Conducting RCTs for rare diseases is challenging because of difficulties relating to achieving optimal sample size and ethical issues about using placebo/ no treatment to one arm.
- Real-world evidence (RWE) studies provide valuable information about rare diseases that can help understand knowledge gaps and plan for RCTs.
- Data from RWE studies can also be used for drug approval for rare diseases, given the challenges in conducting RCTs in such conditions.
- With this background, we were interested in understanding the current trends in research conducted in real-world settings about rare diseases, focusing on studies reported from Asian countries (including India, China, Japan, Korea, Thailand, Malaysia, Singapore, Turkey, Pakistan, Saudi Arabia, Israel, Iran, UAE, Lebanon, and other Asian countries).

Objective

- To explore the trends in rare disease research in RWE setting in Asian countries in the decade between 2013-2023.

Methodology

Eligibility Criteria

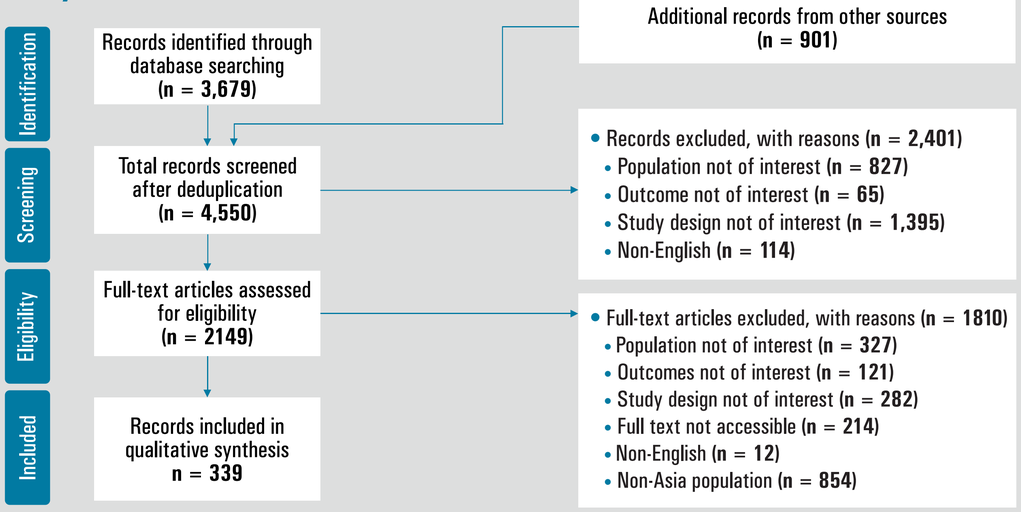
Facet	Inclusion Criteria	Exclusion
Population	Human patients from Asia of either gender and all ages suffering from a condition defined as 'rare disease' or 'orphan disease'	• No human participants • Patients without 'rare disease' or 'orphan disease' • Residing outside Asia
Intervention, Comparators	Any	None

Outcomes	• Demographics: Country, age, gender, genetic/genomic factors
	• Disease related outcomes: Therapy area/ organ system involved
	• Source of information: Type of RWD source, Database/ registry details
	• Area of research:
	  • Epidemiology
	  • Natural history, prognosis and outcomes
	  • Clinical outcomes: efficacy, safety, and other clinical outcomes
	  • Humanistic outcomes: QoL and other PROs
	  • Economic outcomes: burden of disease, cost-effectiveness, HCRU
		Other outcomes

Study design	RWE research, including but not limited to EHR/ EMR data, insurance claims data, registries, administrative data, survey data, observational studies done in the real world setting, pharmacy data, etc	• RCTs, single-arm trials, and any study performed in a restricted setting • In-vitro and in-vivo studies • All non-primary studies, including reviews (narrative, systematic), guidelines, expert opinions, case reports, case series, letters, editorials, commentary, errata, etc
Date range	Starting from 01 Jan 2013 till 31 Dec 2023	Older articles
Language	English	Non-English

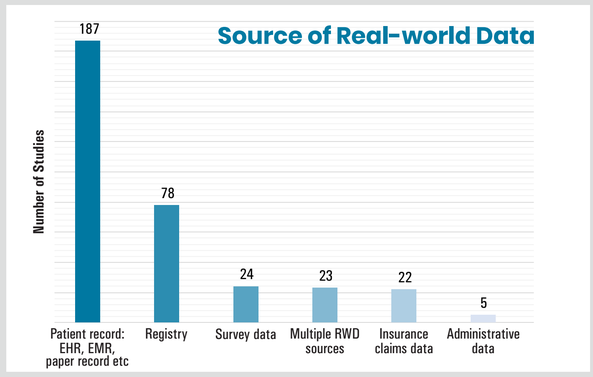
Results

Study selection flowchart



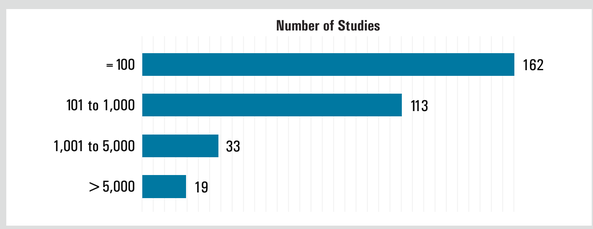
Study design and setting

- Study design
  - Retrospective observational study: 260
  - Cross-sectional study: 29
  - Prospective observational study: 27
  - Case-control study: 19
  - Ambispective observational study: 03
  - Economic analysis: 01
- Number of centres
  - Single centre: 168
  - Multicentre: 171



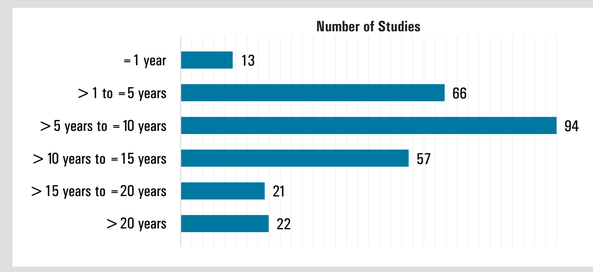
Sample size

- Ranged from 4 to 5,65,050 patients (this was a comprehensive study of all rare diseases in Korea during 2006 to 2018)
- Total: 10,92,032 patients
- Not reported in 12 studies



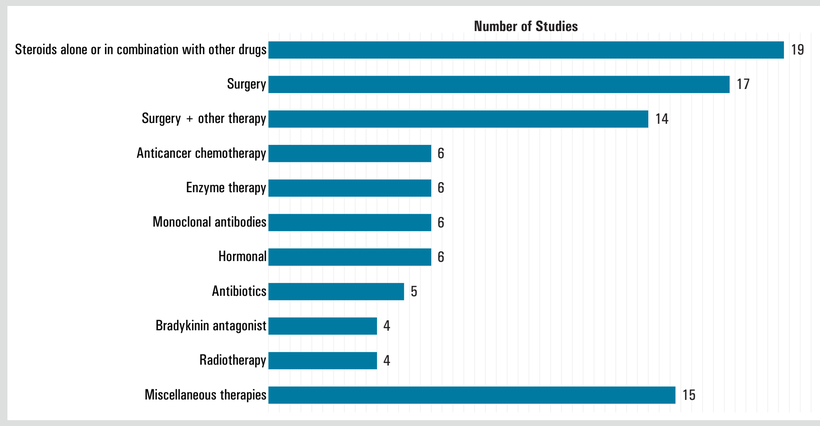
Study Duration

- Study duration as reported in 273 studies, and ranged between 21 days and 35 years.
- Not reported in 66 studies.

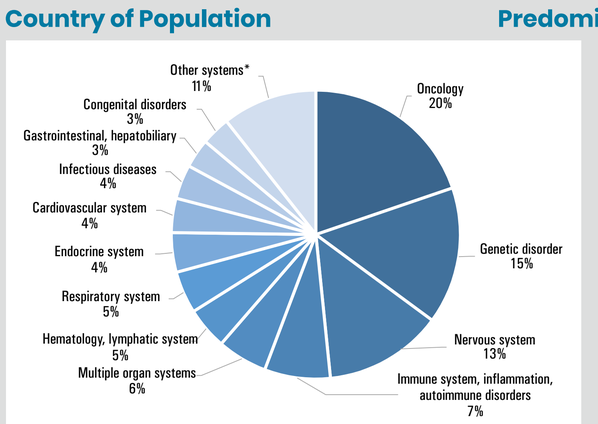


Intervention

- A total of 102 publications described at least one therapeutic intervention administered to treat the rare disease.
- The interventions described varied widely.

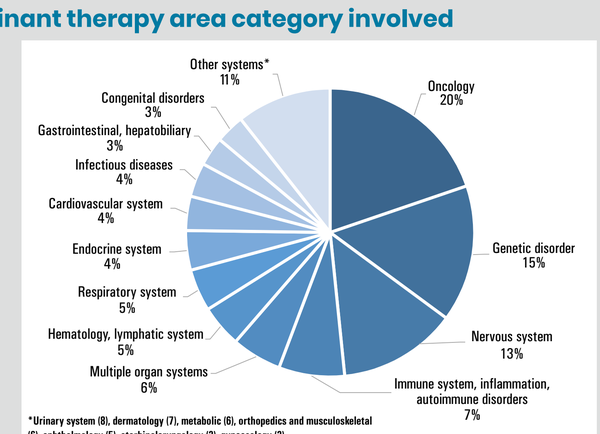


Country of Population



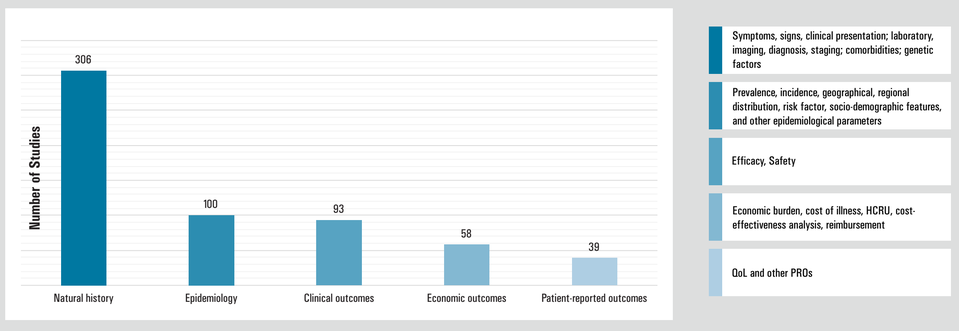
*Saudi Arabia (7), Israel (6), Thailand (3), Malaysia (2), Pakistan, Singapore, Iran, UAE, Lebanon (1 each)

Predominant therapy area category involved



*Urinary system (8), dermatology (7), metabolic (6), orthopedics and musculoskeletal (6), ophthalmology (5), otorhinolaryngology (2), gynaecology (2)

Research trends



Outcomes: Clinical, Humanistic and Economic

Clinical Outcomes

- 93/339 studies reported clinical outcomes of therapy administered to manage the rare disease.
- Efficacy only: 40 studies
- Safety only: 8 studies
- Both efficacy and safety: 45 studies

Patient Reported Outcomes

- Only 39/339 studies reported patient-reported outcomes.
- QoL only: 15 studies
- Other PROs only: 9 studies
- Both QoL and another PRO: 15 studies

Economic Outcomes

- Only 58/339 studies reported economic outcomes including HCRU.
- Economic burden/ cost of illness: 23 studies
- HCRU: 51 studies
- Reimbursement/ insurance premium: 2 studies
- Cost-effectiveness analysis: 1 study

Discussion

- The definition of rare disease depends on the geography as well as the regulator.[2]
  - The USFDA categorizes a disease as rare if it affects fewer than 1:200,000 (i.e., < 0.0005%) in the USA.
  - The EMA uses a definition of fewer than 1:2,000 (i.e., < 0.05%) in the European Union.
- As a result of these varying definitions, the number of conditions categorized as 'rare' is quite large, with some estimates indicating nearly 8000 pathologies falling under this category.[3]
- Thus, even though the number of patients being affected by individual rare disease is lower, the cumulative number of patients worldwide with 'rare diseases' is considerably large.[3]
- Since the overall time and efforts required to complete a retrospective RWE study are generally shorter than a prospective RCT, RWE data are increasingly used in regulatory approval of drugs for rare diseases.[4]
- In our research, the majority of rare disease research in Asia focuses on natural history (90%) and epidemiology (29%).
- Only 27% of the studies (93/339) analyzed clinical outcomes of therapy, indicating an underrepresentation of treatment effectiveness in real-world practice for rare diseases.
- Even fewer studies reported humanistic (11%) and economic (17%) outcomes; thus, the QoL and economic burden of rare diseases remain to be uncovered.
- The high proportion of retrospective studies (76%) reflects the reliance on existing data sources like patient records (EHRs and EMRs) and registries, but this also underscores the need for prospective studies to better understand real-time clinical decision-making and outcomes in rare diseases.
- China, Japan, and Korea dominated the rare disease research landscape, with only 10 studies coming from India. Given India's large population, this number is disproportionately low, highlighting a significant gap in rare disease research within the country.
- International collaboration, while present in 56 studies, remains limited. Expanding multinational research could improve data diversity and increase sample sizes, helping to generalize findings across different populations.
- The highest research concentration is in oncology (20%) and genetic disorders (15%), which may indicate areas of growing interest or particular burden, but also suggests that other rare diseases are less studied.
- While the total patient population across studies was over 1 million, most studies (48%) had sample sizes below 100. This is expected, given the inherent rarity of these conditions, but it underscores the challenge of gathering sufficient data to draw strong, generalizable conclusions. Collaborative and multicenter studies could help address these limitations.

Conclusion

Rare disease research in real-world settings from Asian countries focusses more on natural history of the disease and epidemiology, and less on therapy outcomes and economic impact.

References

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