MAKING A CASE FOR CASE REPORTS:
A SCOPING REVIEW OF THE USE OF AND CHALLENGES WITH CASE REPORT DATA IN QUANTITATIVE SYNTHESIS

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BACKGROUND

- Data derived from case reports and case series have traditionally been considered low-quality evidence due to their anecdotal nature and potential for bias.
- However, case reports provide richer clinical data that may otherwise be lacking. For example, they are key sources of information for the initial identification of adverse events for different therapies, as well as recognition of rare diseases or rare variations of more common diseases.[1]
- These data may be especially informative when consolidated. While systematic literature reviews (SLRs) that include case reports have previously been conducted, these typically use descriptive syntheses that have limited value to inform inferences across individual reports.
- Quantitative synthesis of case report data derived from SLRs may provide additional clinical insights over descriptive synthesis alone; however, formal methodologic guidance for this approach is currently lacking.

OBJECTIVE

This scoping review characterized contemporary methodologies used for quantitatively synthesizing case report data and noted key strengths and limitations.

DISCLOSURES

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METHODS

- This review followed the Joanna Briggs Institute methodological guidance for conducting scoping reviews.[2] Key elements of the research question related to **Population**, **Concept**, and **Context** were defined (**Figure 1**).
- A search strategy was implemented in MEDLINE and Embase in October 2022 using indexed terms and keywords related to case reports/series, SLRs, and meta-analyses.
- Abstracts were screened and articles describing or employing methodologies for quantitative synthesis of case report data were included.
- Study characteristics and approaches were summarized, and the potential benefits and methodologic challenges of quantitative case report syntheses were tabulated.

Figure 1: PCC criteria

Population — Any disease area

Concept — Systematic review with quantitative synthesis of case report data

Context — Methodologies • Guidelines • Limitations • Challenges • Recommendations
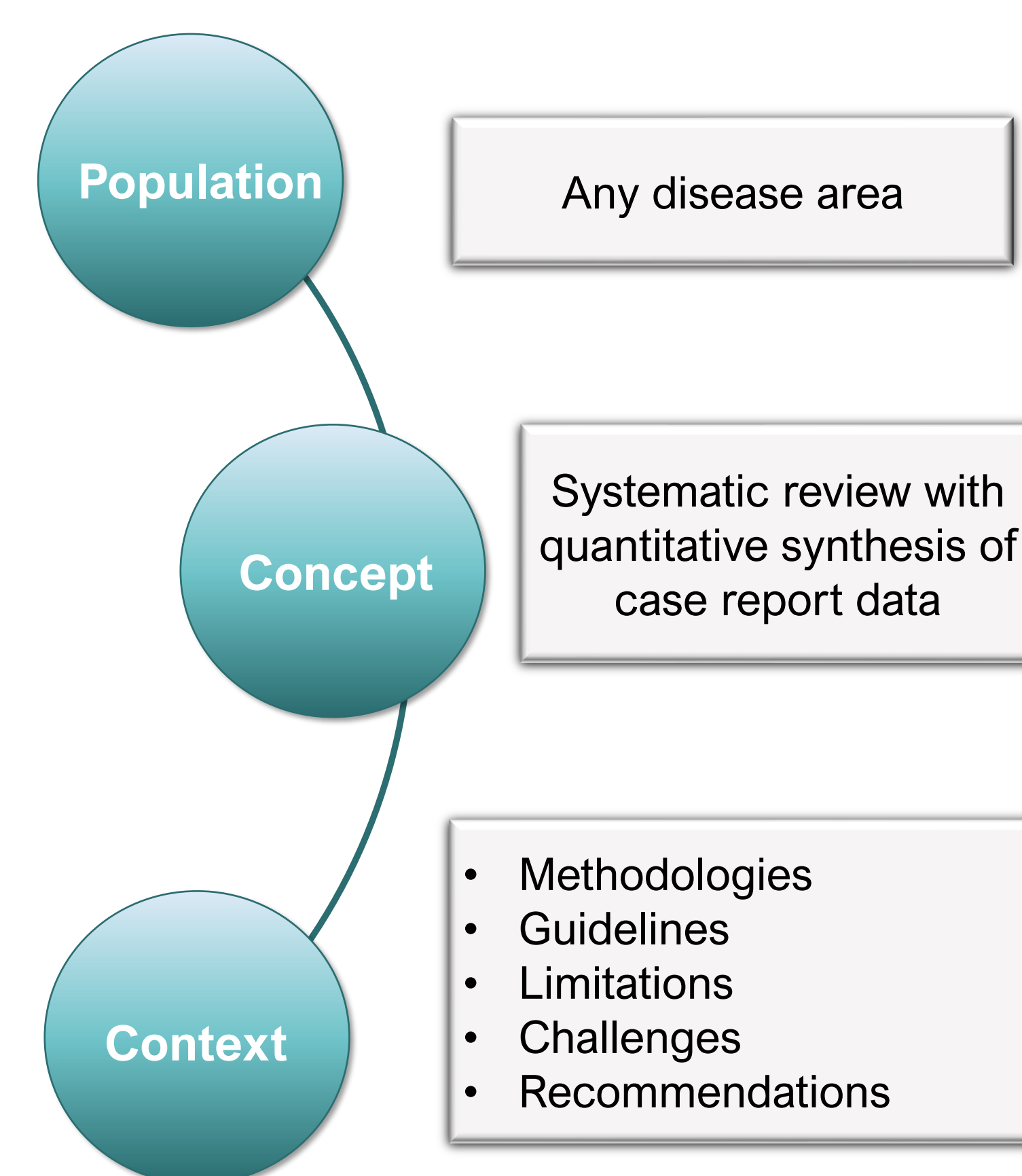
PCC, Population, Concept, Context

RESULTS

- Of 2,235 abstracts identified, 13 (0.6%) were included (**Figure 2**); 10 were SLRs and 3 were methodological articles.
- One article described a critical appraisal tool to assess the methodological quality of case series, which may be relevant for synthesizing data from studies with such designs.
- The majority (60%) of included SLRs investigated rare conditions (ranging from 5-477 patients); however, complications of COVID-19 were also commonly studied (30%, **Table 1**).
- Within SLRs, common quantitative synthesis methods included random effects models (40%), regression analyses (40%), Kaplan-Meier analyses (20%), and odds ratios to characterize risk factors (20%, **Table 1**).
- Across included articles, 6 (46%) highlighted the potential role of quantitative case report synthesis to generate hypotheses, 4 (31%) to identify rare associations, and 2 (15%) to provide richer clinical detail (**Figure 3**).
- Key methodologic challenges included publication bias (46%), clinical heterogeneity of cases (39%) and small sample sizes for individual outcomes (31%, **Table 2**).

Figure 2: PRISMA flow diagram

Table 1: Key characteristics of included articles

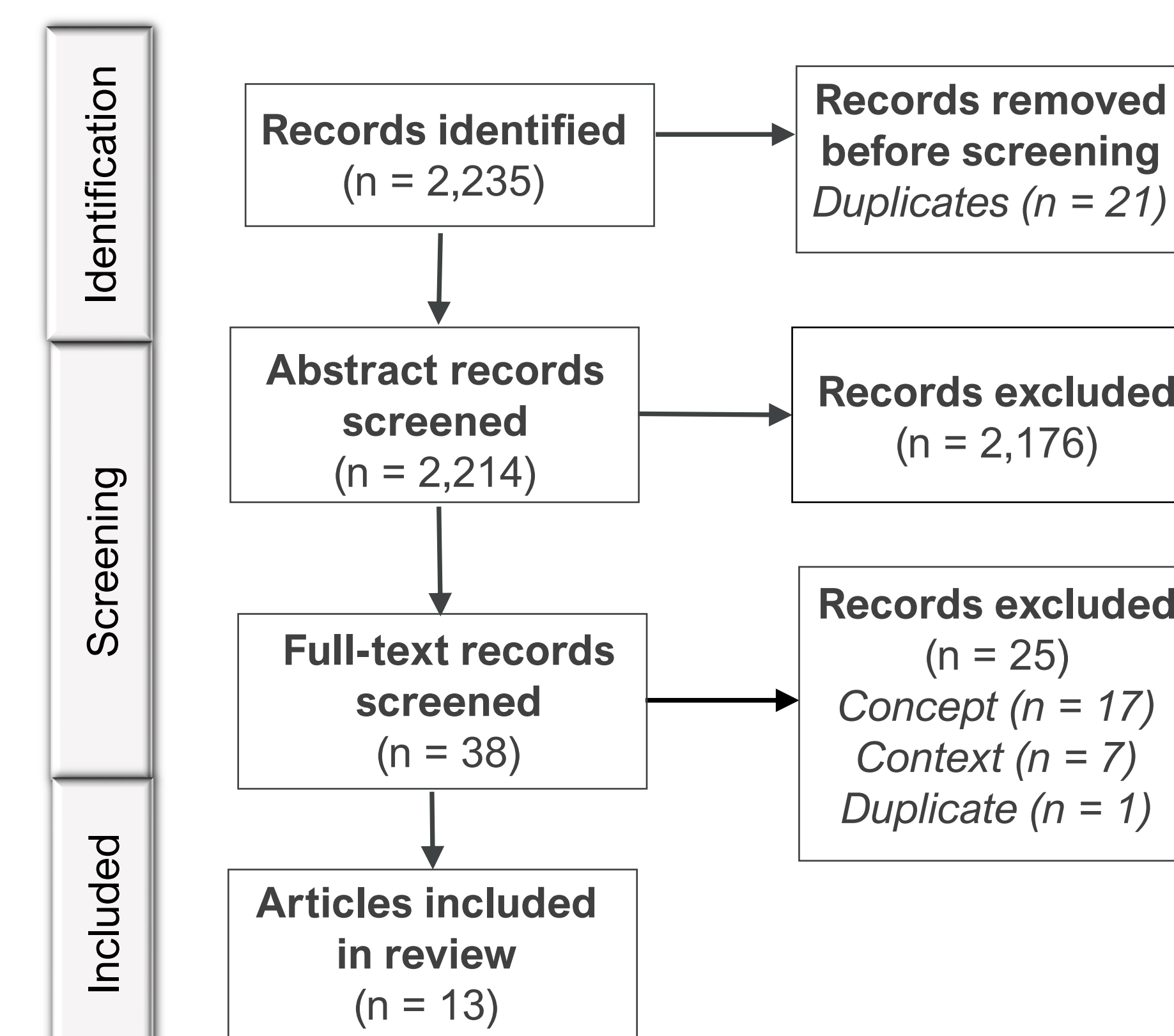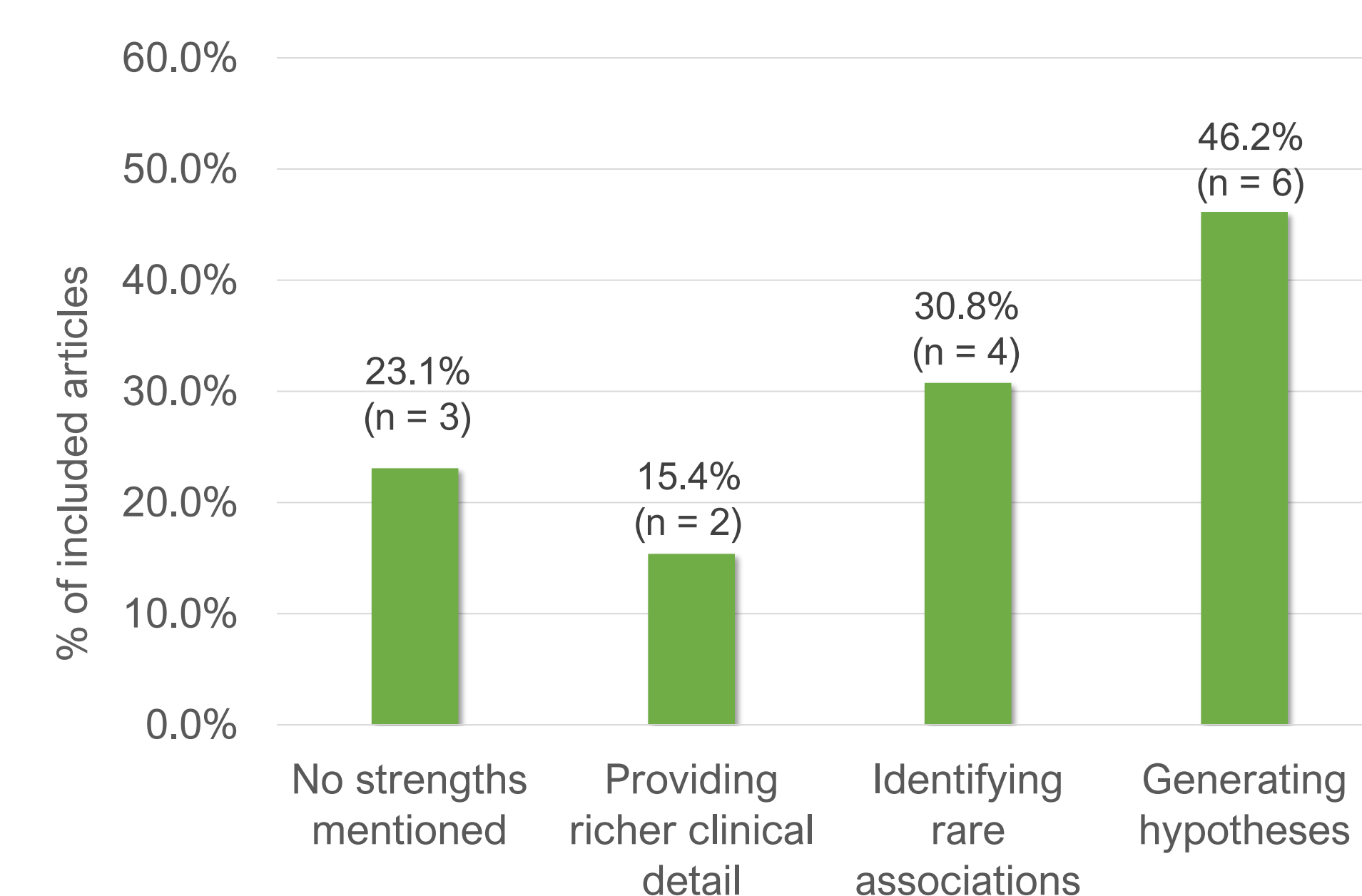| Article	Disease area	Rare condition	Quantitative synthesis approach
Alharbi et al., 2022 (42 patients)	COVID-19 associated with immune thrombocytopenia	No, but novel event	Random-effects model, forest plot
Azab et al., 2021 (5 patients)	Optic neuritis post-COVID	No, but novel event	Odds ratios to characterize risk factors, forest plot
McKnoulty et al., 2020 (39 patients)	Spontaneous renal fornix rupture in pregnancy	Yes	Kaplan-Meier analysis
Munn et al., 2019	NA (methods paper)	No	NA (quality assessment for synthesis of cases)
Murad et al., 2018	NA (methods paper)	No	Fixed- or random-effects models, regression analysis
Nambiema et al., 2021	NA (methods paper)	No	Random-effects model
Rouleau et al., 2012 (477 patients)	Posterior shoulder dislocation	Yes	Odds ratios to characterize risk factors
Sampayo-Cordero et al., 2019 (56 patients)	Mucopolysaccharidosis type II	Yes	Positive/negative predictive value, sensitivity, specificity compared to clinical studies
Trager et al., 2021	Persistent spinal pain syndrome type 2	No	Regression analysis
Venepally et al., 2022 (163 patients)	Nonbacterial thrombotic endocarditis	Yes	Regression analysis
Werneke et al., 2016 (299 patients)	Serotonin syndrome	Yes	Analysis of variance
Yadav et al., 2021 (219 patients)	Re-positive COVID-19 cases	No	Random-effects model
Zhang et al., 2021 (27 patients)	Primary intracranial leiomyosarcomas	Yes	Kaplan-Meier analysis, regression analysis

Figure 3: Strengths of case report synthesis

% of included articles

- No strengths mentioned: 23.1% (n = 3)
- Providing richer clinical detail: 15.4% (n = 2)
- Identifying rare associations: 30.8% (n = 4)
- Generating hypotheses: 46.2% (n = 6)

- Other reported strengths were (multiple strengths may be reported in articles):
- Investigate rare manifestations or outcomes for rare condition (n = 2)
- Use in reviews of effectiveness or provide initial estimates of efficacy for new treatments in rare diseases (n = 2)
- Investigate prevalence and/or incidence/etiology/risk, when there are no other studies to consider (n = 1)
- Investigate rare acute poisonings or preliminary reports of new drugs (n = 1)
- Allow comprehensive integration of all relevant evidence (n = 1)
- Describe a new phenotype or genotype of disease or a new pathogen (n = 1)
- Describe an unknown adverse effect of an existing drug (n = 1)
- Describe a novel treatment for a known condition (n = 1)

Table 2: Challenges of case report synthesis*

Article	None noted	Publication bias	Non-uniform data	Limited number of cases	Not controlled, higher risk of bias	Cannot support causality
Alharbi et al., 2022		✓				
Azab et al., 2021	✓					
McKnoulty et al., 2020		✓				
Munn et al., 2019				✓		
Murad et al., 2018					✓	
Nambiema et al., 2021		✓				
Rouleau et al., 2012			✓			
Sampayo-Cordero et al., 2019			✓			
Trager et al., 2021				✓		
Venepally et al., 2022		✓				
Werneke et al., 2016			✓			
Zhang et al., 2021				✓		

*Other reported challenges were (each reported in one article): lack of generalizability, anecdotal nature or low certainty of the evidence.

CONCLUSION

- This scoping review highlighted common approaches, potential value, and limitations of quantitative evidence synthesis of case report data.
- Such methods may be important in aggregating data on outcomes among those with rare conditions, summarizing infrequent events, or exploring risk factors for these.
- Despite the preliminary nature of this review, the issues identified with synthesizing case report data suggest that guidance is needed to provide greater clarity for rigorously implementing this methodology.
- Future work may characterize the biases of this approach and potential implications of these biases on the derived estimates.

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