Poster Code: HPR26

Certainty of Effectiveness Evidence Supporting Orphan Drug Approvals in China

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1.Background

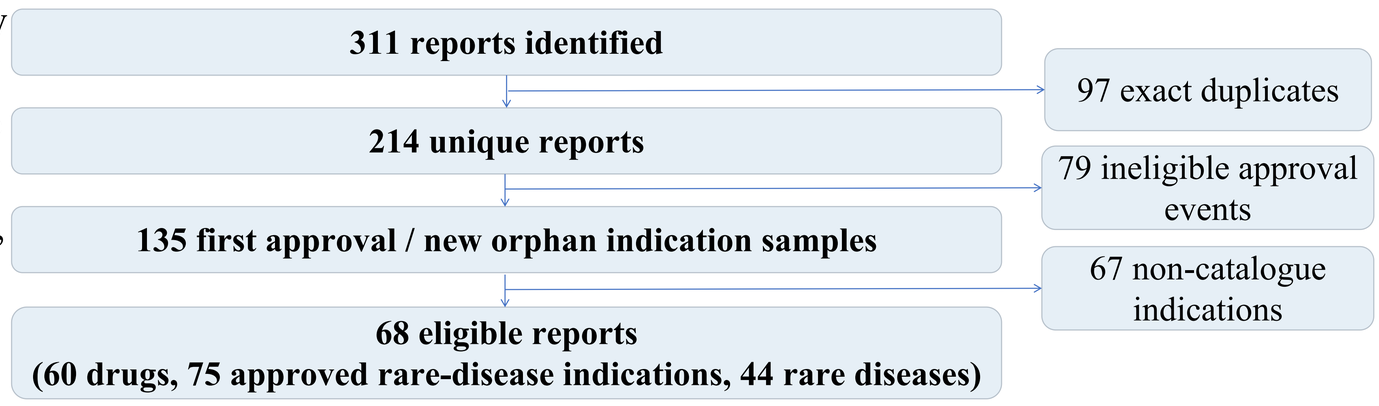
Rare diseases often involve small patient populations and limited clinical evidence, creating substantial uncertainty in drug evaluation. Regulatory flexibility may facilitate timely access to orphan drugs, but the certainty of the supporting effectiveness evidence in China remains unclear.

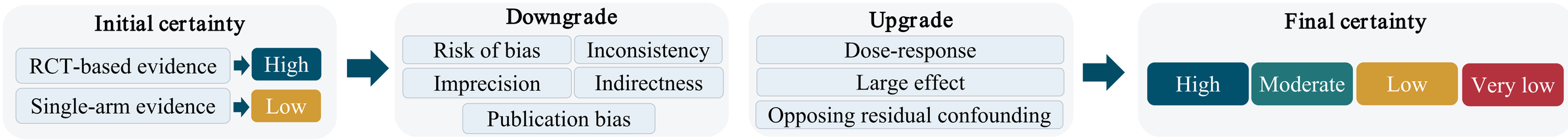
2. Objectives

To assess the certainty of effectiveness evidence supporting orphan drug approvals in China and quantify the main sources of uncertainty.

3. Methods

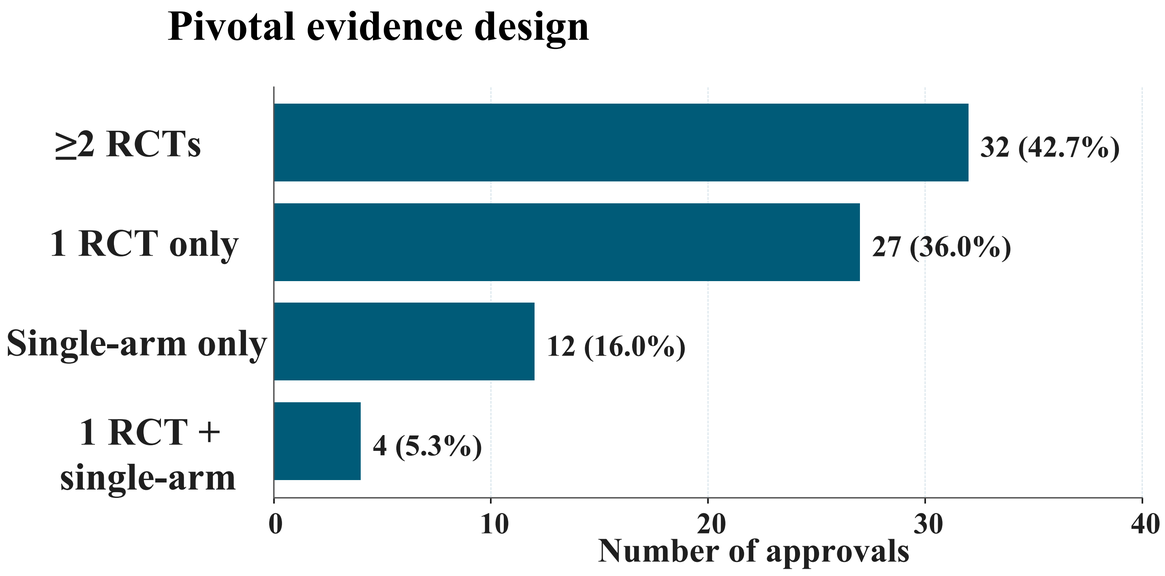
We conducted a retrospective regulatory study using review reports from China's Center for Drug Evaluation. Drugs approved from January 1, 2016 to December 31, 2025 were screened if their approved indications were included in China's national rare disease catalogues. For each approval, pivotal effectiveness evidence was extracted, core study design was classified, and certainty was assessed using a prespecified modified GRADE framework.



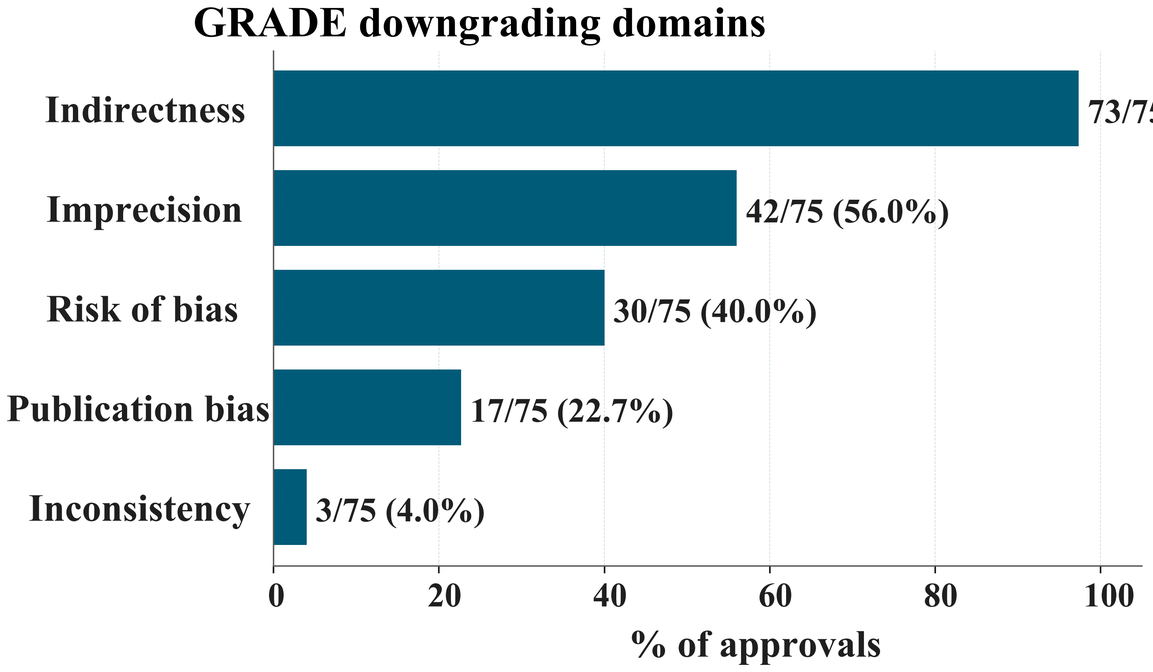


4. Results

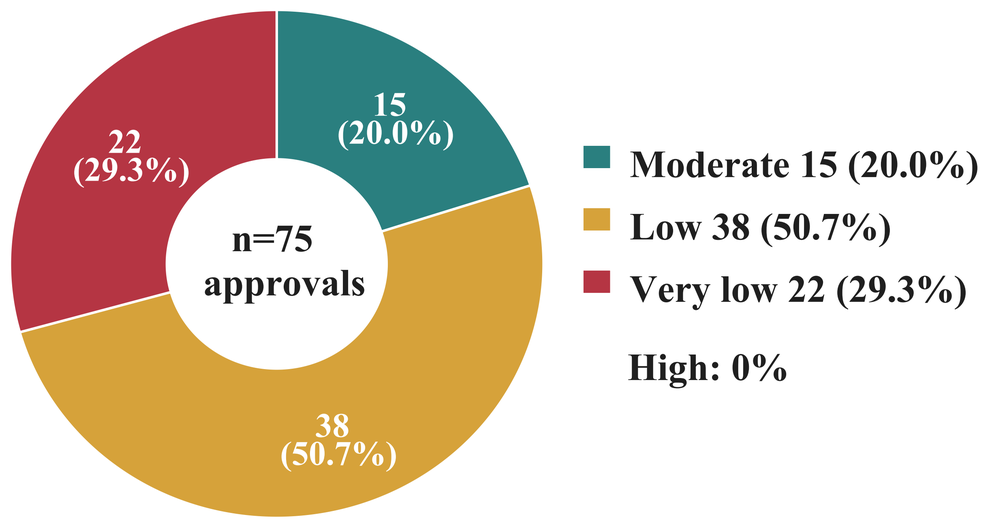
- RCT-based evidence predominated, although 16.0% of approvals relied solely on single-arm studies.



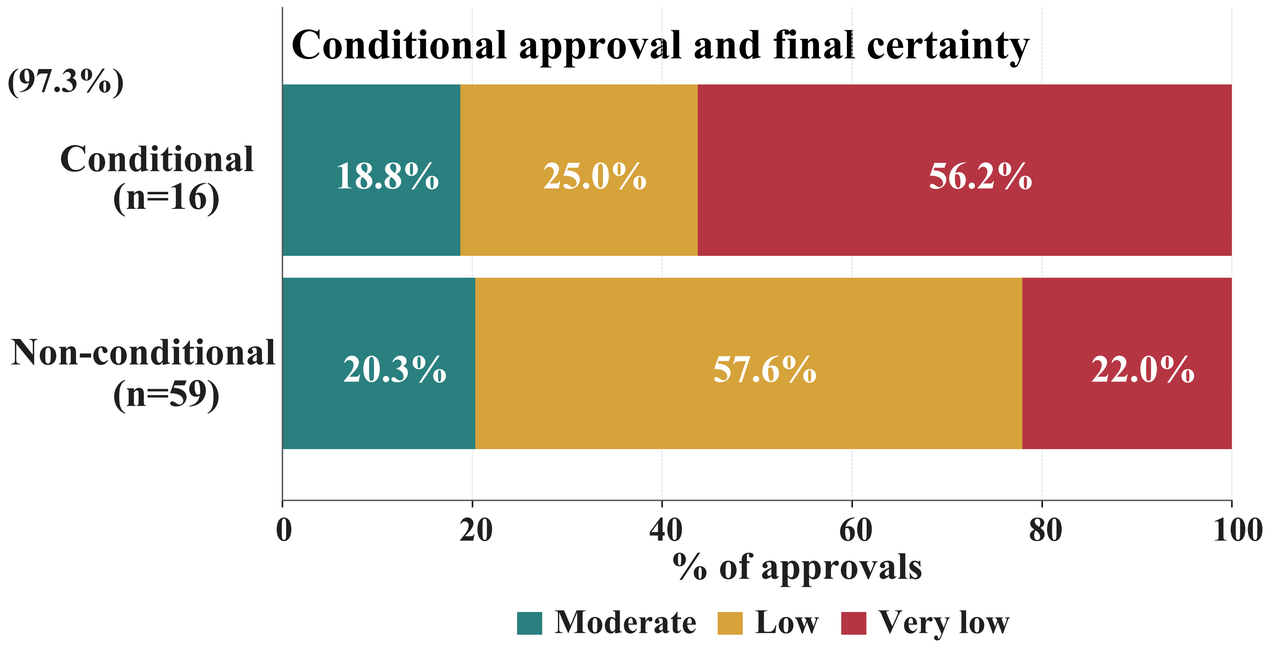
- Indirectness was the most frequent downgrading domain, affecting 97.3% of approvals.



- Overall certainty was limited, with 80.0% of approvals rated as low or very low and none retaining high certainty.



- Very low certainty was substantially more common among conditionally approved indications than non-conditionally approved indications (56.2% vs. 22.0%).



5.Conclusions

The certainty of effectiveness evidence supporting orphan drug approvals in China was generally limited, mainly due to evidence extrapolation, limited Chinese patient data, small samples, and surrogate endpoints. Regulatory flexibility can accelerate access in areas of high unmet need, but should be paired with clearer mechanisms for managing residual uncertainty and indication-specific post-approval evidence generation.

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