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Who Gets Left Out? The Real-World Eligibility Gap in Landmark Metastatic Renal Cell Carcinoma Trials

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Objective:
Pivotal trials in metastatic renal cell carcinoma often enrol selected, relatively fit patients who may not reflect routine clinical practice. We assessed the proportion of real-world patients who would have been ineligible for landmark systemic therapy trials and examined whether eligibility status was associated with clinical outcomes.

Methods:
Two complementary PubMed searches were conducted from database inception to 17 July 2026. Eligible observational studies applied criteria from pivotal phase II or III systemic therapy trials to adults with advanced or metastatic renal cell carcinoma treated in routine practice. Overlapping cohorts were identified, and only the largest or most informative report was retained. Trial-ineligibility proportions were pooled using a random-effects logit model. Survival and treatment outcomes were synthesised narratively because therapies, eligibility criteria and effect measures varied. Risk of bias was assessed using the Joanna Briggs Institute cohort appraisal framework.

Results:
Ten unique cohorts comprising 6,146 patients were included. The pooled prevalence of trial ineligibility was 46.9% (95% confidence interval [CI] 36.2–57.9%; I^2=98.4%). In a sensitivity analysis excluding the PRINCIPAL study, where missing measurable-disease information contributed substantially to non-eligibility, the pooled estimate fell to 41.6% (95% CI 34.9–48.7%; I^2=95.7%). Common reasons for exclusion included poor performance status, non-clear-cell histology, brain metastases, anaemia, renal impairment and laboratory abnormalities. Six of seven comparative cohorts reported poorer survival among trial-ineligible patients, whereas one prospective cohort found broadly comparable treatment outcomes. Risk of bias was moderate in seven studies and high in three.

Conclusion:
Approximately two in five patients treated for metastatic renal cell carcinoma in routine

practice would not have qualified for the landmark trials that established current standards of care. Trial-ineligible patients generally had poorer outcomes, although substantial heterogeneity and residual confounding limit causal interpretation. Future trials should justify restrictive criteria, broaden eligibility where clinically appropriate and report outcomes for commonly excluded patient groups.