A New Tool for Flagging Imbalanced Adverse Events of Potential Interest

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Disclosure

David Kerr and Li Zhou are employees of Axio Research, LLC, a CRO that provides biostatistical support for clinical studies.

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Background and Objectives

- Medical reviewers want to focus on those events that have imbalances
- Lengthy tables provide motivation for an automated way to flag imbalances worthy of clinical review
- Neither p-values nor odds ratio alone can tell the complete story
- Calls for a tool that incorporates both p-value and odds ratio

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Standard Adverse Events Reporting

Incidence of Adverse Events (Number of Subjects) by SOC and PT

System Organ Class Preferred Terms	Treatment A (N=1000)	Treatment B (N=1000)	Total (N=2000)
Blood and lymphatic system disorders	79 (7.9%)	58 (5.8%)	137 (6.9%)
Anaemia	60 (6.0%)	46 (4.6%)	106 (5.3%)
Anaemia macrocytic	0 (0.0%)	1 (0.1%)	1 (0.1%)
Eosinophilia	3 (0.3%)	0 (0.0%)	3 (0.2%)
Hilar lymphadenopathy	0 (0.0%)	1 (0.1%)	1 (0.1%)
Hypochromic anaemia	2 (0.2%)	0 (0.0%)	2 (0.1%)
Iron deficiency anaemia	2 (0.2%)	3 (0.3%)	5 (0.3%)
Leukocytosis	2 (0.2%)	0 (0.0%)	2 (0.1%)
Lymphadenitis	0 (0.0%)	1 (0.1%)	1 (0.1%)
Lymphadenopathy	1 (0.1%)	2 (0.2%)	3 (0.2%)
Nephrogenic anaemia	3 (0.3%)	1 (0.1%)	4 (0.2%)
Pancytopenia	0 (0.0%)	1 (0.1%)	1 (0.1%)
Polycythaemia	1 (0.1%)	0 (0.0%)	1 (0.1%)
Spontaneous haematoma	1 (0.1%)	0 (0.0%)	1 (0.1%)
Thrombocytopenia	4 (0.4%)	2 (0.2%)	6 (0.3%)

This output continues for 63 more pages!

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The Kerr Statistic

- Incorporates both p-value and odds ratio into a common scale
- Defined, in the simplest form, as:
  - $\log_{10}$(p-value) + abs($\log_{10}$(odds ratio))
- Critical Values
  - > 1.50 : mild difference
  - > 1.60 : moderate difference
  - > 1.70 : strong difference
  - **> 1.80** : very strong difference

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Examples (Balanced Randomization)

Arm A: Count out of N=100	Arm B: Count out of N=100	P-value	OR	Kerr-stat
1	5	0.212	0.192	1.391
1	6	0.118	0.158	1.727
2	7	0.170	0.271	1.337
2	8	0.101	0.235	1.627
2	9	0.058	0.206	**1.920**
10	2	0.033	5.444	**2.217**
10	3	0.082	3.593	1.643
10	4	0.164	2.667	1.211
10	20	0.073	0.444	1.486
10	21	0.049	0.418	1.685
10	22	0.033	0.394	**1.890**
20	9	0.043	2.528	1.767
20	10	0.073	2.250	1.486
20	32	0.076	0.531	1.396
20	33	0.054	0.508	1.563
20	34	0.038	0.485	1.736

Examples (Imbalanced Randomization)

Arm A: Count out of N=100	Arm B: Count out of N=200	P-value	OR	Kerr-stat
1 (1.0%)	10 (5.0%)	0.107	0.192	1.686
1 (1.9%)	11 (5.5%)	0.067	0.174	**1.932**
2 (2.0%)	14 (7.0%)	0.100	0.271	1.567
2 (2.0%)	15 (7.5%)	0.064	0.252	1.795
10 (10.0%)	7 (3.5%)	0.032	3.063	**1.981**
10 (10.0%)	8 (4.0%)	0.067	2.667	1.597
10 (10.0%)	37 (18.5%)	0.064	0.489	1.502
10 (10.0%)	38 (19.0%)	0.047	0.474	1.657
10 (10.0%)	40 (20.0%)	0.032	0.444	**1.841**
20 (20.0%)	21 (10.5%)	0.032	2.131	**1.827**
20 (20.0%)	22 (11.0%)	0.051	2.023	1.599
20 (20.0%)	62 (31.0%)	0.054	0.556	1.522
20 (20.0%)	63 (31.5%)	0.040	0.544	1.660
20 (20.0%)	64 (32.0%)	0.030	0.531	1.799

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Why Not Just Use P-value

- Two scenarios:
  - 1/100 vs. 6/100

    p-value = 0.12; might be of potential interest
  - 50/100 vs. 62/100

    p-value = 0.12; not necessarily of interest
- Similar p-values
- Difficult to find critical value to flag the events

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Why Not Just Use Odds Ratio

- Two scenarios:
  - 15/100 vs. 30/100

    OR = 0.41; might be of potential interest
  - 3/100 vs. 7/100

    OR = 0.41; not necessarily of interest
- Similar odds ratios
- Difficult to find critical value to flag the events

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Example of Results (Tabular) – AEs with Kerr-Stat > 1.70 included

Preferred Terms / System Organ Class	Treatment A N=1000	Treatment B N=1000	Kerr Statistic	Odds Ratio	Fisher's Exact P-value
Hyperkalaemia	249 (24.9%)	333 (33.3%)	4.545	0.66	0.000
Hypotension	59 (5.9%)	102 (10.2%)	3.540	0.55	0.001
Otitis media	0 (0.0%)	9 (0.9%)	3.420	0.10	0.004
Metabolism and nutrition disorders	406 (40.6%)	481 (48.1%)	3.197	0.74	0.001
Diabetes mellitus	29 (2.9%)	10 (1.0%)	2.982	2.96	0.003
Diabetic foot	1 (0.1%)	10 (1.0%)	2.943	0.10	0.012
Hypoglycaemia	46 (4.6%)	79 (7.9%)	2.776	0.56	0.003
Abscess limb	7 (0.7%)	0 (0.0%)	2.717	8.06	0.015
Haematuria	2 (0.2%)	12 (1.2%)	2.681	0.16	0.013
Myocardial ischaemia	9 (0.9%)	1 (0.1%)	2.632	9.07	0.021
VIIth nerve paralysis	0 (0.0%)	6 (0.6%)	2.356	0.14	0.031
Retinopathy	6 (0.6%)	0 (0.0%)	2.356	7.04	0.031
Gastroenteritis viral	8 (0.8%)	1 (0.1%)	2.319	8.06	0.039
Dyspnoea exertional	8 (0.8%)	1 (0.1%)	2.319	8.06	0.039
Arteriosclerosis	7 (0.7%)	1 (0.1%)	2.004	7.04	0.070
Cardio-respiratory arrest	1 (0.1%)	7 (0.7%)	2.004	0.14	0.070
Periodontitis	0 (0.0%)	5 (0.5%)	1.987	0.17	0.062
Weight decreased	0 (0.0%)	5 (0.5%)	1.987	0.17	0.062
Left ventricular hypertrophy	5 (0.5%)	0 (0.0%)	1.987	6.03	0.062
Osteoporosis	2 (0.2%)	9 (0.9%)	1.845	0.22	0.065
Peripheral arterial occlusive disease	9 (0.9%)	2 (0.2%)	1.845	4.53	0.065

The original 64 pages of output has been reduced to one page!

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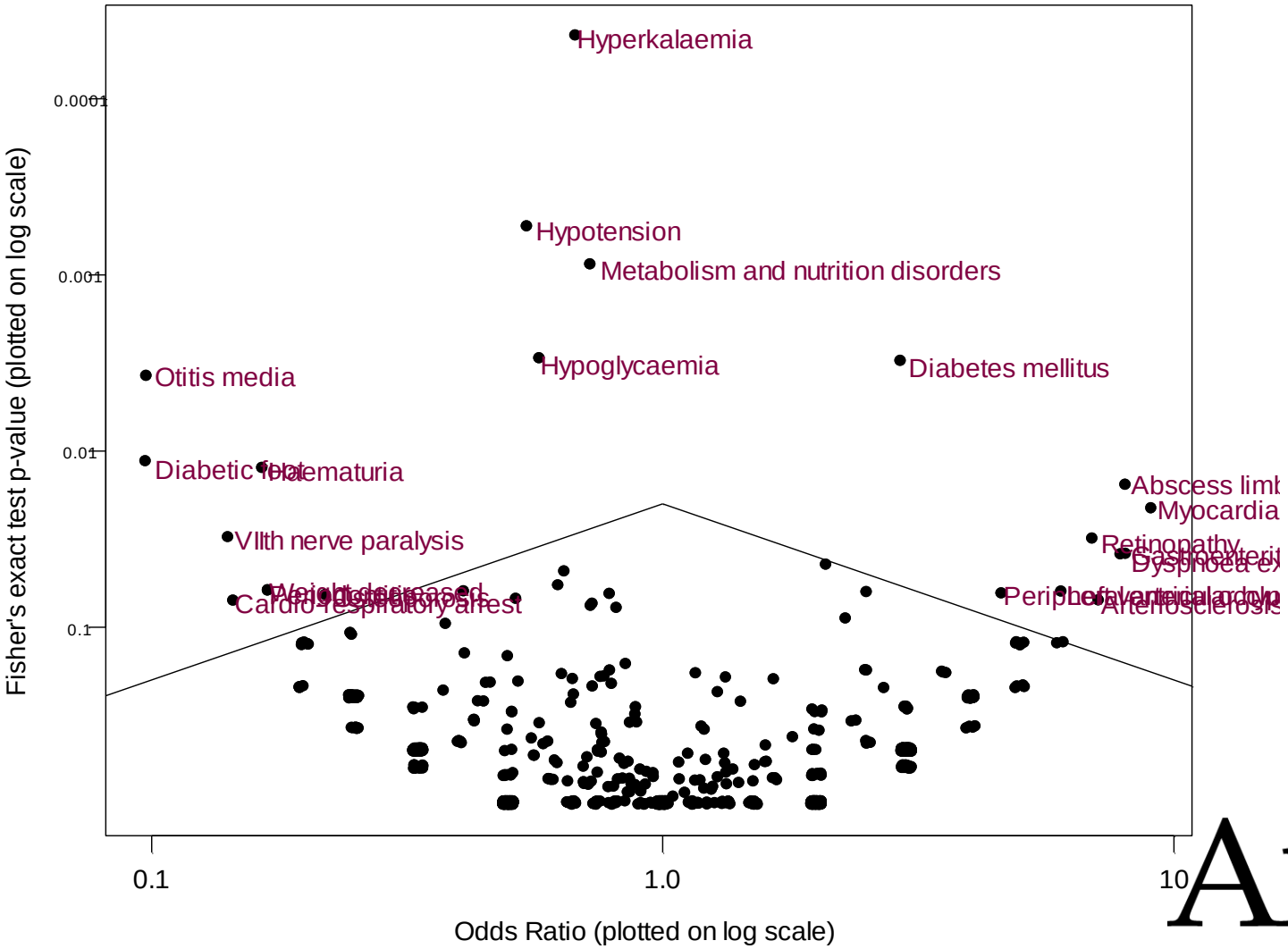
Example of Results (Graphical) - AEs with Kerr-Stat >1.70 annotated



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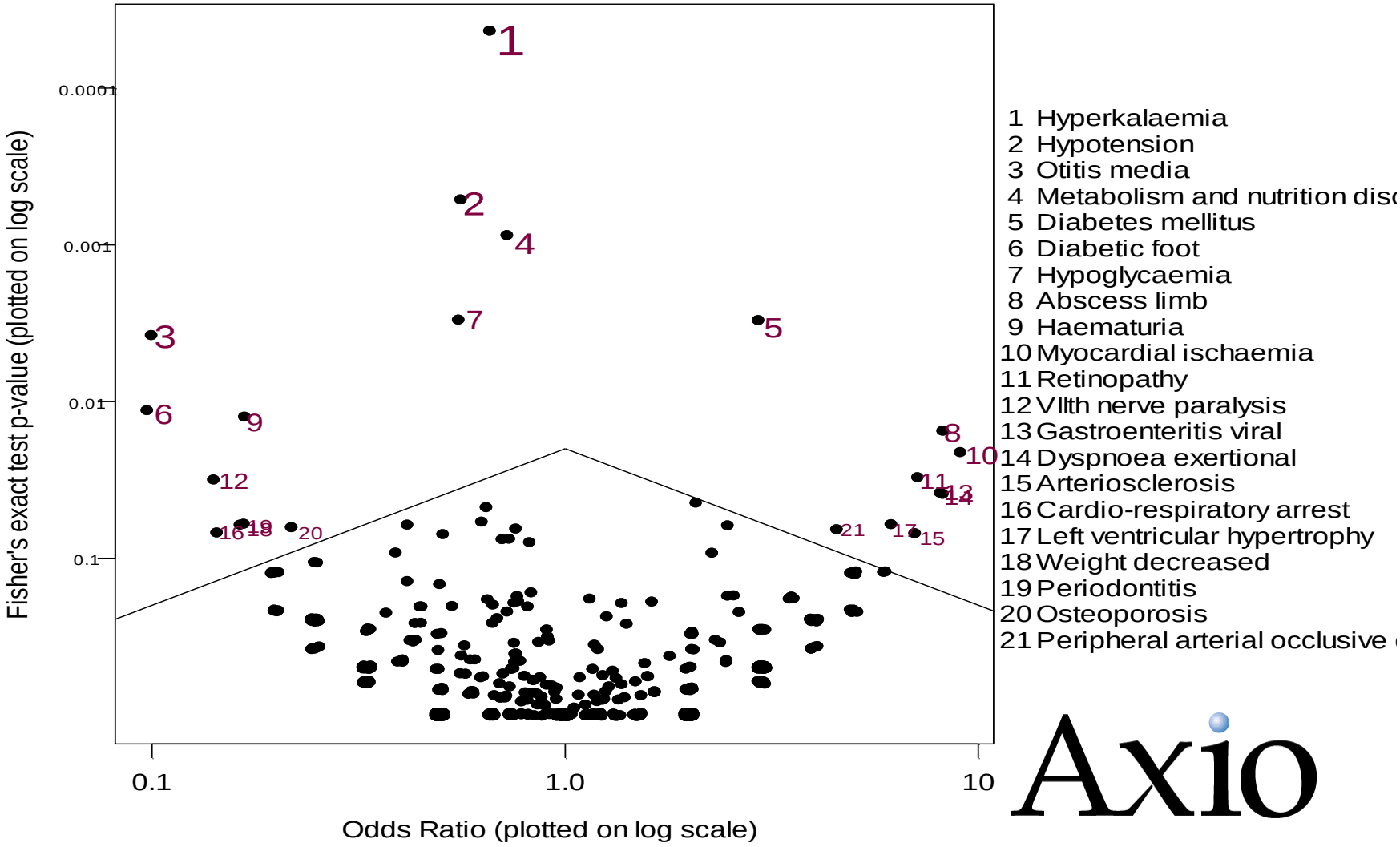
Example of Results (Graphical) - AEs with Kerr-Stat >1.70 annotated



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Extensions

- Formula can be adjusted:

  - $\log_{10}$(p-value) + **A** * abs($\log_{10}$(odds ratio))

  – Medical reviewer can determine which component is of more interest.

  – As A approaches 0, the p-value takes priority (flatter '^' in the figure).

  – As A gets larger, the odds ratio takes priority (more pointed '^' in the figure).

- More than two treatment arms

  – Get Kerr statistics for any pair of treatment arms

  – Flag an event if any of the Kerr statistic is greater than the critical value

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Conclusions and Limitation

- This useful tool allows a medical reviewer to concentrate only on imbalanced events of potential interest
- This tool incorporates both the odds ratio and the p-value to flag events
- This approach works well for both events that occur in large numbers and events that occur relatively infrequently
- The medical reviewer can set the critical value that controls for how conservative the filtering is based on whether they are interested in seeing more terms or fewer terms.
- Statistical inference from the table or Kerr statistics is not valid

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Thank you

Thank you for your attention!

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