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The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes

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Abstract

Words: 178 (max 200)

Objective: To present a novel and simple graphical approach to improve the presentation of the treatment ranking in a network meta-analysis (NMA) including multiple outcomes.

Study Design and Settings: NMA simultaneously compares many relevant interventions for a clinical condition from a network of trials, and allows ranking of the effectiveness and/or safety of each intervention. There are numerous ways to present the NMA results, which can challenge their interpretation by research users. The rank-heat plot is a novel graph that can be used to quickly recognize which interventions are most likely the best or worst interventions with respect to their effectiveness and/or safety for a single or multiple outcome(s), and may increase interpretability.

Results: Using empirical NMAs, we show that the need for a concise and informative presentation of results is imperative, particularly as the number of competing treatments and outcomes in a NMA increases.

Conclusions: The rank-heat plot is an efficient way to present the results of ranking statistics, particularly when a large amount of data is available, and it is targeted to users from various backgrounds.

Keywords: multiple treatment meta-analysis; multiple outcomes; probability best; SUCRA; graphical displays; presentation results

Words: 4,696

What is new?

- A particularly useful feature of network meta-analysis (NMA) is the ability to rank the effectiveness and safety of each intervention in the model for each outcome.
- There are numerous ways to present the results of a NMA, which can challenge the interpretation by research users. Another challenge is the multitude of results from the NMA, which makes it difficult to present all of the data in a single table or figure in a way that is easy to interpret by the readers.
- We propose the rank-heat plot, a novel and simple graphical approach to improve the presentation of results from the treatment ranking analysis for multiple outcomes.
- The rank-heat plot can be used to quickly recognize what are most likely the best and worst interventions with respect to their effectiveness and/or safety in a single or multiple outcome(s), and can identify treatments that have not been studied with regard to particular outcomes.
- Clinicians can use the rank-heat plot to discuss which agent is optimal across the different outcomes with their patients, guideline developers can use it to inform their recommendations, as can policy makers decide about drug coverage.

1 Introduction

2 Network meta-analysis (NMA) allows the synthesis of data from a network of
 3 randomised controlled trials facilitating the simultaneous comparison of many
 4 interventions for managing a specific clinical condition. The advantages of NMA (e.g.,
 5 ranking multiple competing interventions according to their effectiveness and/or safety [1-
 6 3]) have increased its application over the last two decades [4]. However, there are
 7 numerous ways to present NMA results [5-9], and this variation makes their interpretation
 8 difficult for research users [10]. Presentation of NMA results becomes even more
 9 challenging when large numbers of interventions and outcomes are included. Since the
 10 treatment ranking might vary across different outcomes, it is necessary to include all NMA
 11 results to make an informed decision about the 'best' available treatment. Several graphical
 12 displays have been suggested to present the ranking results of all competing treatments
 13 evaluated in a NMA. Hawkins et al [11] were early proponents of presenting the ranking of
 14 treatments in a plot (which we later call the 'bubble plot') showing the probability of each
 15 treatment being the most effective, the second most effective, etc. Cipriani et al [12] used
 16 rankograms to present the distribution of probabilities of each treatment being ranked at
 17 each of the possible positions. Salanti et al [5] developed two alternative ways to
 18 graphically depict the treatment ranking to facilitate presentation and interpretation of
 19 NMA results, including the stacked bar plots and the cumulative ranking probability plots.
 20 The latter authors also suggested the use of the surface under the cumulative ranking
 21 (SUCRA) curve as an alternative way to rank the treatments, which was a significant
 22 advancement in summarizing the NMA findings [5]. Tan et al [7] have proposed the
 23 summary forest plot matrix, displaying the NMA and pairwise meta-analysis treatment
 24 effect estimates, the heterogeneity estimates, and the ranking and probability best statistics.
 25 The authors suggest that pie and rank charts can be used as complementary methods to the
 26 summary forest plot matrix to visually summarize the intervention ranking. An approach to
 27 summarize the NMA findings of more than one outcome has previously been presented in
 28 rankograms, where types of lines correspond to different outcomes [12]. Two-dimensional
 29 scatterplots have also been presented in the literature to depict the ranking of treatments for
 30 two different outcomes [6, 13]. However, to the best of our knowledge, there no graphical
 31 tools available to summarize the ranking statistics of all studied NMA outcomes in a single
 32 plot.

33 The aim of this study is to present a novel and simple graphical approach to
 34 improve the presentation of results from the treatment ranking for multiple outcomes in
 35 NMA. We also discuss approaches that have been suggested to present treatment ranking.

36 Datasets

37 We use three previously published systematic reviews and NMAs to present
 38 different approaches for the graphical representation of the ranking statistics. The
 39 illustrative examples represent small (3 outcomes and eight treatments [14]), medium (5

outcomes and 15 treatments [15, 16], and large (5 outcomes and 30 treatments [17]) databases with respect to the number of treatments and outcomes studied in NMA. Details of these datasets are provided in Text S1 in Supporting Information.

Graphical tools for treatment ranking

Different graphical displays have been developed to present the ranking results of all competing treatments included in a network. In this paper, we present the graphical approaches for treatment ranking that have been used in published NMAs [4]. The NMA findings can be summarized using the following statistics: 1) mean/median treatment ranking, 2) probability for each treatment in a NMA being the best ($P(\text{best})$), and 3) the surface under the cumulative ranking (SUCRA) curve.

Plots for a single outcome

Most graphical tools, including pie charts, rank charts, rankograms, bar plots, bubble plots, and SUCRA plots can present ranking statistics for a single outcome. Pie and rank charts can be produced when SUCRAs, $P(\text{best})$, or median/mean rankings are available for a specific outcome. Rankograms, bar plots, bubble plots, and SUCRA plots can only be produced when all ranking probabilities for each treatment being considered at each position are available for each outcome.

Pie chart

A pie chart can graphically depict the treatment ranking in a NMA. The area of the circle in a pie chart is divided into T different parts, with T number of treatments in the network. Each region is proportional to the respective ranking probability. The bigger the segment, the better the ranking of the treatment for that outcome.

In Figure S1a we present the probability for each long-acting inhaled agent being the safest for chronic obstructive pulmonary disease (COPD) with respect to arrhythmia. This suggests that salmeterol/fluticasone is most likely the best with 38.98% probability to rank first, whereas formoterol/budesonide is the least likely to rank first (probability=0.58%).

Rank chart

In the rank chart [7], the treatments are ordered from greatest to lowest probability of being the best. In Figure S1b we present the treatment order according to $P(\text{best})$ for arrhythmia for the COPD NMA, using a color intensity scheme to highlight what is most likely the best treatment. The colored rank chart uses light grey at the top of the chart with the highest $P(\text{best})$ and dark grey at the bottom of the chart to indicate the lowest $P(\text{best})$.

Rankogram

A rankogram is a two-way plot that shows the ranking probabilities of a treatment on the y-axis that correspond to each of the T positions presented on the x-axis [12]. For a

specific treatment and outcome, connecting the probabilities against the rank positions yields a rankogram. The greater the curve bends near the origin, the better the treatment.

In Figure S2, the ranking probabilities are presented for each of the 12 COPD long-acting inhaled agents for each of the 12 possible positions. The rankograms summarize the expected rank order of the treatments included in the arrhythmia network. Salmeterol/fluticasone is most likely the safest, as it is associated with the largest probabilities among all 12 competitors to rank at the first treatment position and has the higher curve near the origin. In contrast, vilanterol/fluticasone has a 3.46% probability to rank 1st, and is associated with the highest probability (68.59%) among all competing treatments to rank 12th.

Stacked bar plot

Stacked bar plots show the corresponding probabilities for the treatments involved in a network to rank at each of the T positions. On the x-axis, the T ranking positions are presented, and on the y-axis, the ranking probabilities are shown. Each vertical bar depicts the probabilities of the T treatments being at the specific rank position. Each treatment uses a portion of the bar proportional to the probability of being at the corresponding rank position. The greater the area in a bar, the higher the probability of the treatment being at the corresponding rank position [5].

In Figure S3, we present the ranking probabilities for the 12 long-acting inhaled agents using a stacked bar plot. Salmeterol/fluticasone is most likely the safest treatment, as it yields the largest area in the bar that corresponds to rank 1 with respect to arrhythmia. Contrastingly, vilanterol/fluticasone yields a small probability (3.46%) to rank 1st corresponding to a small area of the first bar, whereas it is most likely the least safe as indicated by the largest area for the 12th bar.

Bubble plots

A bubble plot shows the ranking for all treatments at each possible rank and presents T possible ranking positions on the x-axis against the treatments included in the network on the y-axis [11]. Each point corresponds to three pieces of information: treatment, rank position, and probability of each ranking. The area in each circle is proportional to the ranking probability, and the number in each circle represents the probability for the corresponding treatment to rank at the specific position.

Figure S4 demonstrates the bubble plot for the ranking probabilities of the 12 long-acting inhaled treatments for arrhythmia. This plot suggests that salmeterol/fluticasone has a 38.98% probability of being the safest and a 0.21% probability of being the least safe. Similarly, vilanterol/fluticasone has a 3.46% probability of ranking 1st and a 68.59% probability of ranking 12th.

SUCRA plots

SUCRA plots [5], also known as ‘cumulative ranking probability plots’, show probabilities of a treatment amongst k best treatments, where k ranges from 1 to T. Salanti

et al. [5] suggest summarizing the ranking probabilities using the SUCRA values (expressed in percentages) that can be calculated from the cumulative ranking curves. The larger the area under the curve, the better the treatment.

In Figure S5, we present the SUCRA values and curves for the 12 long-acting inhaled agents for arrhythmia [17]. These results show that the SUCRA for salmeterol/fluticasone of being the safest for arrhythmia is 74.80%, whereas vilanterol/fluticasone has the least probability of being the best (SUCRA=14.10%).

Plots for multiple outcomes

There are two graphical tools for multiple outcomes; scatterplots and the rank-heat plot (the new graphical tool we are proposing). A scatterplot can only be used when outcome data is available for the same treatments, whereas the rank-heat plot can be used regardless of whether outcome data are available for all treatments. Both plots can be produced for SUCRAs, P(best), or median/mean rankings.

Scatterplot

The relative ranking for two outcomes has been presented in two-dimensional scatterplots [6], which can be extended to three-dimensional plots presenting the treatment ranking across three outcomes. Clustering methods have been suggested to group the performance of treatments according to their efficacy and/or safety, using the cluster ranking plot [6].

Figure S6 shows the ranking of 15 serotonin (5-HT₃) receptor antagonists according to SUCRA values for nausea and vomiting in a cluster ranking plot. The different colors and circles represent the different groups of treatments according to their similarity with regard to their performance in both outcomes. For example, the cluster of treatments on the right upper corner (in blue) represents treatments that perform well in both outcomes, whereas the cluster of treatments close to the origin (in red) are the treatments that perform the worst on both outcomes (placebo in this case).

Rank-heat plot

The rank-heat plot is a novel approach for the visual presentation of the treatment hierarchy across multiple outcomes. A rank-heat plot includes N circles with the same center but different radii, where N is the number of outcomes. The area of each concentric circle is divided by the total number of treatments T, and each sector is colored according to the ranking of the particular treatment at the corresponding outcome. The scale consists of the transformation of three colors (red, yellow and green) and ranges from the lowest to the highest value of the ranking statistic, such as 0% to 100% according to the SUCRA values. The red color corresponds to the smallest SUCRA value (0%), values near the middle of the scale are yellow, and the green color corresponds to the highest SUCRA value (100%). It should be noted that only the color of the sector is interpretable and that the area of the sector does not convey any information.

Figure 1 displays the hierarchy of 8 treatments for type I diabetes across 3 outcomes (Figure 1a), as well the treatment order of 15 5-HT₃ agents across 5 outcomes (Figure 1b) using the rank-heat plot. Uncolored sectors suggest that data on that outcome was not reported for the particular treatment in the trials included in the NMA. Figure 1a suggests that glargine twice daily (bid) is most likely the the best treatment for severe hypoglycemia, whereas glargine once daily (od) performs well for both A1_C and weight gain outcomes. For severe hypoglycemia, detemir [od] is one of the best agents, but as the dosage frequency increases, the performance of detemir decreases. Overall, detemir[od/bid] performs best for weight gain. For A1_C, detemir [od/bid] and detemir four times daily (qid) have a similar good performance, whereas detemir [od] performs worst among the three. In Figure 1b, granisetron+dexamethasone is most likely the most effective for preventing nausea, vomiting, and postoperative nausea and vomiting combined, but it performs worst for arrhythmia.

(Figure 1 here)

A rank-heat plot can also be presented using a grey scale of colors with dark grey corresponding to the smallest SUCRA value (0%) and light grey corresponding to the highest SUCRA value (100%). A star symbol in white sectors refer to treatments without data on the outcome within the circle.

(Figure 2 here)

The datasets for our illustrative examples and the R code used to create the rank-heat plots are available in Texts S1 and S2 in Supporting Information. The rank-heat plot provides also the option of a colored version, where each color is associated with a different pattern (see Figure S7). This version of the rank-heat plot has been also tested for use by people with color blindness.

Discussion

Ranking statistics for treatments included in a NMA can be displayed in various graphs. A comparison of the methods according to their properties is shown in Table 1. We have proposed a new way to present the treatment ranking in NMA with multiple outcomes. A rank-heat plot is a graphical presentation of the NMA results and can be used to quickly recognize what are most likely the best and worst interventions with respect to their effectiveness and/or safety in a single or multiple outcome(s), which may increase interpretability. It can also identify treatments that have not been studied with regard to particular outcomes. Clinicians can use this information to discuss which agent is optimal across the different outcomes with their patients and caregivers, guideline developers can use this to inform their recommendations, as can policy makers decide about drug coverage. The novel approach may improve presentation and facilitate interpretation of findings. Hence, the rank-heat plot could be added to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guideline extention for NMA [10].

A limitation of the suggested graph is that it cannot display all of the ranking probabilities for each treatment and outcome at each position. However, the rank-heat plot is an efficient way to present the results of ranking statistics, particularly when a large amount of data is available. As well, it can be used to compare treatment ranking results across different statistical models. Heatmap plots can poorly discriminate between values close to each other, such as SUCRA=90% and SUCRA=80%. However, the rank-heat plot provides the option of including the exact values in each sector. Similar to all other approaches, all outcomes in the rank-heat plot have equal weights (i.e., no outcome preferences are taken into account) and no numerical summary of all outcomes is provided.

(Table 1 here)

Although some of the statistics examined here have inherent strengths and limitations [5, 18, 19] (e.g., the P(best) does not account for the uncertainty in the treatment effect estimates), our focus is on the graphical presentation of these statistics and we do not discuss their strengths and limitations. Our purpose is to provide an approach overcoming one of the key limitations of the current approaches, and more specifically to provide a strategy for easily displaying and understanding all of the available information on safety and effectiveness. In addition, we do not discuss the interpretability of the different graphical presentations; an area warranting further research. Finally, it is beyond the scope of this study to consider graphical ways of presenting the treatment effects and their uncertainty (e.g., forest plots) estimated in a NMA. It would be helpful to assess how investigators in previous studies report the NMA results and handle this complexity when more than two outcomes are evaluated, which would benefit from an extensive systematic review of all published NMAs. More importantly, research is needed to assess the understanding of the available approaches for presenting the treatment ranking by clinicians, guideline developers, and policy makers. This research is critical because different approaches may complicate inference and decision-making based on NMA findings.

Authors' contributions

AAV, SES, AF and ACT conceived and designed the study. AF and AAV designed the code used for the analysis. AAV wrote the first draft manuscript and the other authors edited the manuscript.

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Competing interests

Drs. Tricco A.C. and Straus S.E. are on the editorial board of the Journal of Clinical Epidemiology, but were not involved with the peer review process or decision for publication. The other authors have nothing to declare.

Abbreviations

A1c: glycosylated hemoglobin, ACLI: acclidinium bromide, AZD3199: AZD3199 (ultra LABA), BECL/FORM: beclomethasone/formoterol, bid: twice daily, BUDE: budesonide, COPD: chronic obstructive pulmonary disease, DOLA: dolasteron, DOLA+DEX: dolasetron + dexamethasone, DOLA+DROP: dolasetron + droperidol IV, FLUT: fluticasone, FLUT/TIOT: fluticasone/tiotropium, FORM, formoterol, FORM/BUDE: formoterol/budesonide, FORM/TIOT/BUDE: formoterol/budesonide/tiotropium, FORM/MOME: formoterol/mometasone, FORM/TIOT: formoterol/tiotropium, GLYC: glycopyrronium bromide, GRAN: granisetron, GRAN+DEX: Granisetron + Dexamethasone, GRAN+DROP: dolasetron + droperidol IV, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, INDA/TIOT: indacaterol/tiotropium, MOME: mometasone, NMA: network meta-analysis, Od: once daily, ONDA: ondansetron, ONDA+DEX: ondansetron + dexamethasone, ONDA+DROP: ondansetron + droperidol IV, ONDA+MET: Ondansetron + Metoclopramide IV, PALO: palonosetron, PALO+DEX: Palonosetron + Dexamethasone, P(best): Probability of being the best, PLAC: placebo, PONV: postoperative nausea and vomiting, RAMO: ramosteron, qid: four times daily, SAML: salmeterol, SALM/FLUT: salmeterol/fluticasone, SALM/TIOT: salmeterol/tiotropium, SUCRA: surface under the cumulative ranking curve, TIOT: tiotropium, TIOT/BUDE/FORM: tiotropium/budesonide/formoterol, TIOT/FLUT/SALM: tiotropium/ fluticasone /salmeterol, TIOT+Resp: Tiotropium Respimat (Soft Mist Inhaler), TRIAM: triamcinolone acetonide, TROP: tropisetron, UMEC: umeclidinium, VILA: vilanterol, VILA/FLUT: vilanterol/fluticasone, VILA/UMEC: vilanterol/umeclidinium

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Tables and Figure captions

Table 1. Overview of the properties of the graphical tools presenting the ranking statistics for a single or multiple outcomes

	Single Outcome						Multiple Outcomes	
	Pie chart	Rank chart	Rankogram	Stacked bar plot	Bubble plot	SUCRA plots	Scatter-plot	Rank-heat plot
P(best) can be displayed	✓	✓	✓	✓	✓	✓	✓	✓
SUCRA can be displayed	✓	✓	--	--	--	✓	✓	✓
Mean/Median ranks can be displayed	✓	✓	--	--	--	--	✓	✓
All ranking probabilities (or cumulative probabilities) can be displayed	--	--	✓	✓	✓	✓	--	--
Can display the ranking of many (>15) treatments	--	✓	✓	--	✓	✓	✓	✓
The exact numerical values of the ranking statistics can be presented	✓	--	✓	--	✓	--	✓	✓
Can identify treatments that have been studied only in certain outcomes	--	--	--	--	--	--	--	✓
More than 3 outcomes can be displayed	--	--	--	--	--	--	--	✓
Can be produced when different treatments are included in the studied outcomes	✓	✓	✓	✓	✓	✓	--	✓

Figure 1. Rank-heat plots of 8 treatments studied in patients with type 1 diabetes in three different outcomes (a) and 15 serotonin (5-HT₃) receptor antagonists for patients undergoing surgery in five outcomes (b). Each sector is colored according to the SUCRA value of the corresponding treatment and outcome. The scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%). In (b) each sector includes also the SUCRA value corresponding to the specific treatment and outcome. Uncolored sectors show that the underlying treatment was not included in the NMA for the particular outcome.

Figure 2. Rank-heat plot of 30 COPD agents ordered according to their SUCRA values in five different outcomes. Each sector is colored according to the SUCRA value of the corresponding treatment and outcome. A dark grey corresponds to the smallest SUCRA value (0%) and a light

grey corresponds to the highest SUCRA value (100%). Uncolored sectors including a start symbol show that the underlying treatment was not included in the NMA for the particular outcome.

Abbreviations in Figures: A1c: glycosylated hemoglobin, ACLI: acclidinium bromide, AZD3199: AZD3199 (ultra LABA), BECL/FORM: beclomethasone/formoterol, bid: twice daily, BUDE: budesonide, COPD: chronic obstructive pulmonary disease, DOLA: dolasteron, DOLA+DEX: dolasetron + dexamethasone, DOLA+DROP: dolasetron + droperidol IV, FLUT: fluticasone, FLUT/TIOT: fluticasone/tiotropium, FORM, formoterol, FORM/BUDE: formoterol/budesonide, FORM/TIOT/BUDE: formoterol/budesonide/tiotropium, FORM/MOME: formoterol/mometasone, FORM/TIOT: formoterol/tiotropium, GLYC: glycopyrronium bromide, GRAN: granisetron, GRAN+DEX: Granisetron + Dexamethasone, GRAN+DROP: dolasetron + droperidol IV, INDA: indacaterol, INDA/GLYC: indacaterol/glycopyrronium, INDA/TIOT: indacaterol/tiotropium, MOME: mometasone, Od: once daily, ONDA: ondansetron, ONDA+DEX: ondansetron + dexamethasone, ONDA+DROP: ondansetron + droperidol IV, ONDA+MET: Ondansetron + Metoclopramide IV, PALO: palonosetron, PALO+DEX: Palonosetron + Dexamethasone, PLAC: placebo, PONV: postoperative nausea and vomiting, RAMO: ramosteron, qid: four times daily, SAML: salmeterol, SALM/FLUT: salmeterol/fluticasone, SALM/TIOT: salmeterol/tiotropium, SUCRA: surface under the cumulative ranking curve, TIOT: tiotropium, TIOT/BUDE/FORM: tiotropium/budesonide/formoterol, TIOT/FLUT/SALM: tiotropium/ fluticasone /salmeterol, TIOT+Resp: Tiotropium Respimat (Soft Mist Inhaler), TRIAM: triamcinolone acetonide, TROP: tropisetron, UMEC: umeclidinium, VILA: vilanterol, VILA/FLUT: vilanterol/fluticasone, VILA/UMEC: vilanterol/umeclidinium

Supporting Information

Text S1

Datasets used for the three empirical examples (type I diabetes, serotonin (5-HT₃) receptor antagonists for patients undergoing surgery, Chronic Obstructive Pulmonary Disease).

Text S2

R code for rank-heat plot, along with a help file.

Figures

Figure S1. Pie chart and rank chart (b) representing the probability for each treatment being the best in the chronic obstructive pulmonary disease (COPD) arrhythmia network.

Figure S2. Rankograms for the 12 chronic obstructive pulmonary disease (COPD) treatments studied in arrhythmia outcome.

Figure S3. Stacked bar plot for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome.

Figure S4. Bubble plot for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome.

Figure S5. SUCRA plots for the 12 chronic obstructive pulmonary disease (COPD) treatments for arrhythmia outcome.

Figure S6. Cluster ranking scatterplot for 15 serotonin (5-HT₃) receptor antagonists according to SUCRA values for nausea (x-axis) and vomiting (y-axis) outcomes for patients undergoing surgery.

Figure S7. Rank-heat plot of 15 serotonin (5-HT₃) receptor antagonists for patients undergoing surgery in five outcomes. Each sector is colored according to the SUCRA value of the corresponding treatment and outcome. The scale consists of the transformation of three colors red (0%), yellow (50%), and green (100%), and each color is associated with a different pattern. Uncolored sectors show that the underlying treatment was not included in the NMA for the particular outcome.

A. Type I diabetes

B. 5-HT3 surgery

COPD - Rank-heat plot based on SUCRA