DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM

Date: November 25, 2009

To: Wiley A. Chambers, MD, Acting Director of the Division of Anti-Infective and Ophthalmology Products (DAIOP), Office of New Drugs (OND), HFD-520

Through:

Norman Stockbridge, MD, Director of the Division of Cardiovascular and Renal Products (DCRP), OND, HFD-110 and

Stella Machado, PhD, Director Division of Biometrics VI (DBVI), Office of Biostatistics (OB), Office of Translational Science (OTS), HFD 705

Subject: Medical Officer's Consultative Reanalysis of the Febrile Neutropenia Studies of NDA 50-679 using the Multivariate Bayesian Logistic Regression Safety Data Mining method – Assessment of risk of death and risk factors associated with death

Dates:

Data Submissions: May 30, 2008, July 30, 2009, and August 29, 2009

Contract for the Multivariate Bayesian Logistic Regression (MBLR) software awarded*: September 18, 2008

Established Name: Cefepime, Therapeutic Class: Anti-infective, Applicant: Bristol-Myers Squibb Company

Review Issued by: Ana Szarfman, M.D., Ph.D., Medical Officer, DCRP, OND, HFD-110; and DBIV, OB, OTS, HFD-705

*Contract to support the methodology in this review: #1047767 for $19,600; Principal Investigator: Ana Szarfman, M.D., Ph.D., Medical Officer

1. Executive Summary

The Division of Anti-Infective and Ophthalmology Products officially requested Dr. Szarfman's help to understand a reported statistically significant mortality imbalance with cefepime and febrile neutropenia (FN) in two meta-analyses by Paul, Yahav et al and by Yahav, Paul et al.(1,2).The marketed drug cefepime is a mainstay therapy for patients with fever and neutropenia.

The goals of this review are four-fold:

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1. Study the death effect and the subgroups at risk as part of a consultative Medical Officer's review of the cefepime FN data

2. Study these effects by using a new Multivariate Bayesian Logistic Regression (MBLR) method that analyses multiple predictors (covariate-defined subgroups) at once and borrows strength from other issues to correct for multiplicity and small counts, in an automated fashion (further down there is a discussion of this method in plain English)

3. Validate the consistency of the MBLR results by performing sensitivity analyses by choices of covariates and issues in 25 different MBLR runs

4. Describe the lessons learned

The clinical part of this review was done in collaboration with Dr. Peter Kim from the Division of Anti-Infective and Ophthalmology Products (DAIOP). This review also benefited from technical discussions with Dr. Jonathan G. Levine from the Officer of the Commissioner about the automation of particular processes and analyses.

Dr. Ana Szarfman had access to the raw data from 9 febrile neutropenia studies that were originally collected by the sponsor in many different formats. The original raw data were from studies conducted many years earlier. The collection of the data by the sponsor in many different formats is a common occurrence and underscores the need for standard data collection and format.

To perform this review, Ana Szarfman recommended the transformation of these data into standardized Study Data Tabulation Model of the Clinical Data Interchange Standards Consortium (SDTM CDISC) data. The sponsor, Bristol-Myers Squibb (BMS) complied and transformed the data before submission. Ana Szarfman discovered that the data standards are still not comprehensive enough, and that all the different types of deaths (deaths while under active treatment, deaths occurring after the active treatment is stopped) were not properly represented using SDTM CDISC standards.

To automate the analysis of the cefepime data, Ana Szarfman and the contractor created a new Preferred Term named "Death" to represent all types of deaths identified by Peter Kim and Ana Szarfman as valid deaths.

Ana Szarfman also discovered other data issues problems that required correction (further down in Section 4.5.3 of the appendices there is a detailed description of the data problems that this reviewer faced, and how Ana Szarfman addressed these problems).

Using the data in SDTM CDISC standards, we analyzed 30-day all cause mortality and subgroups at risk in the 9 FN studies submitted by the applicant in SDTM CDISC standards using the novel MBLR method.

In the pool of 9 studies, death was higher in the cefepime arm [73/890 (8.2%) than in the comparator arm [41/626 (6.6%)] (Table 2). The risk ratio was 1.25.

The 9 studies we analyzed were mostly small studies powered to answer efficacy questions. These studies were not powered to answer mortality differences and subgroups at risk of dying. Five (5) of the 9 studies enrolled fewer than 120 patients per study (Table 1).

The small size of the studies made them vulnerable to the problem of small counts and multiple comparisons issues.

Taking into account the 1:1 randomization of study ai411131 and the 2:1 randomization of study ai411186, these studies had 14 (15.6%) and 20 (9%) more patients, respectively in the cefepime arm than expected by the enrollment numbers in the comparator arm. Such high disproportion with comparator patients was not seen in other studies. Study ai411186 was an acute leukemia (AL) study (Table 1) The AL patients are expected to have a higher acute risk of death than Solid tumor (ST) patients.

Indeed, the cefepime patients seem to have been sicker *at baseline.* There were 6.25% additional cefepime patients with AL *or* bone marrow transplant (BMT) at baseline. These covariates are associated with acute risk of death. They included 61.7% on cefepime (549/890) and 55.4% on comparator (347/626).

These studies had 9.1% additional cefepime patients who ***did not receive*** concomitant antimicrobial medication (AMM). They included 48% on cefepime (428/890)] and 39% on the comparator (244/626)].

Cefepime deaths tended to occur earlier in the beginning of the treatment or later than comparators in the end of the observation period (page 80).

In the original review of these studies completed on June 12, 1997, the reviewers Drs. David Ross (clinical reviewer) and Aloka Chakravarty (statistical reviewer) chose to analyze the baseline and treatment arm of the first episode of FN.

In this review, if more than one episode of FN occurred, we analyzed the study drug assigned to each patient during the most recent episode of FN relative to death, and the baseline for the corresponding first day of the most recent episode of FN. If only one episode of FN occurred, we analyzed the treatment and baseline assigned to each patient during the first episode (essentially the only episode of FN). We named this type of analysis "Last episode of FN" or "Most recent episode of FN" relative to death. In this report, we use these terms interchangeably.

The multiple episodes of FN, the repeat re-randomization of these patients, and the small size of these studies, made these studies vulnerable to an unbalanced number of covariates by treatment.

The MBLR Method

In plain English, the MBLR estimates would be similar to the "weighted average of the subgroup effect and the overall effect" described in a recent article by Dr. Janet Wittes (3).

MBLR also addresses the task of analyzing multiple responses and multiple covariates at once, and uses shrinkage to help prevent false positives.

MBLR performs at once, pooled data assessments over multiple studies and multiple covariates considered medically important and over multiple medically related events, and corrects for multiplicity and small counts.

This hierarchical Bayesian model could be reformulated as a non-Bayesian random effects model, where the response-by-predictor interaction terms would be viewed as random effects.

To perform this review, Ana Szarfman implemented a functional prototype of a novel MBLR data mining method developed by Dr. William DuMouchel, who provided technical advice.

MBLR is an enhanced form of pooled-data meta-analysis. MBLR performs pooled-data meta-analysis of complete subject level data in the SDTM CDISC format. It addresses a widespread need to correct for multiplicity and small counts when assessing CT safety data.

Using the data in SDTM CDISC standards and the novel MBLR method, we analyzed the probability of death up to 30-day post-treatment for multiple covariates, and estimated adjusted death effects by borrowing strength from other issue(s). We also estimated the corresponding unadjusted effects. MBLR generated these estimations in an automated fashion.

Adjusted Estimates

The adjusted estimates for the 'Death' issue across 25 MBLR runs did not indicate the presence of a statistically significant large death effect for cefepime vs. comparators.

In every one of the 25 MBLR runs the Bayesian effect for 'Death' shrunk toward 1, and it happened regardless of the covariates and issues we put in the model. The adjusted confidence intervals (CI) of each of the covariate-defined subgroups overlapped the adjusted overall CI for each MBLR run and the CIs included 1.

Regardless of the number and types of predictors that we used in the 25 MBLR runs, we never observed an EBOR05[1] >1 for the overall of each run or for any of the predictors (or covariates) that we studied in each run (Table 9 and Figures starting in section 3.3.1.1 on page 48 and in section 4.14 on page 97).

The overall EBOR values across the 25 MBLR runs were 1.162 [1.162 (0.731, 1.848)] *or lower* and the CIs included 1, reaching in some runs with fewer predictors, EBOR values that were very close to 1.

When we simplified the model by removing the covariates that were showing the most overlapping values by covariate within the comparator arm only, we gained precision.

We obtained the widest confidence when we selected to analyze 14 covariates. We obtained the narrowest confidence limits when we reduced the number of covariates from 14 to 7 or less.

Unadjusted Estimates

The unadjusted estimates (OR[2]) for the 'Death' issue were larger than the adjusted (EBOR) ones, and with much wider confidence intervals, as seen when comparing the estimates in Table 10 and Table 11 and Figure 22 and Figures starting on page 97 and on page 140.

The unadjusted overall estimates for the 'Death' issue across 25 MBLR runs did not indicate the presence of a statistically significant large death effect. Every CI for the overall estimates in 25 MBLR runs included 1.

The simplification of the covariate model generated tighter confidence intervals with overall OR values of 2.129 (0.858, 5.285) *or lower* with CIs that included 1.

Each of the covariate-defined subgroups had CI for OR values that overlapped the overall OR values of each MBLR run and in general the CIs included 1.

The unadjusted estimates for the following covariates show an OR05>1 when certain covariates were included in the model, *but not when fewer or more covariates were in the model* (further down in Section 3.3.1.2 of the Medical Officer's Consult Review there is a detailed description).

> 'White race', Study ai411204', 'Solid tumor (Y)', 'Acute leukemia (Y)', 'Age =<60', Neutropenia (3) <=100.

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[1] EBOR, Empirical Bayesian Odds Ratio;
EBOR05, a value such that there is approximately a 5% probability that the true Odds Ratio lies below it;
EBOR95, a value such that there is approximately a 5% probability that the true Odds Ratio lies above it.
[2] OR, Odds Ratio;
OR05, a value such that there is approximately a 5% probability that the true Odds Ratio lies below it
OR95, a value such that there is approximately a 5% probability that the true Odds Ratio lies above it

The unadjusted estimates are subject to the multiple comparison issues. One such example is the finding of an OR05>1 for the age category <=60 years, not detected in the age category >60 years in any of the 25 MBLR runs. This finding is not consistent with biological plausibility.

Conclusions

Our adjusted EBOR results corrected for multiplicity and small counts across 25 different MBLR runs, do not support the reported statistically significant mortality imbalance for FN in two meta-analyses of secondary data (1,2) that triggered the official consult requested by DAIOP.

The overall adjusted EBOR for deaths across 25 different MBLR runs show no evidence for a statistical increase risk of death in FN patients treated with cefepime vs. comparators. The overall EBOR values were 1.162 [1.162 (0.731, 1.848)] *or lower* and the CIs included 1, reaching in some cases EBOR values that were very close to 1.

The adjusted EBOR values for 14 death predictors across 25 MBLR runs show no evidence of an increased risk for cefepime in any subgroup analyzed. The adjusted EBOR values for any of the 14 different death predictors were not significantly greater for cefepime than for the comparators, and the CIs included 1.

The simplification of the covariate model generates tighter confidence intervals, but no predictor that shows EBOR05>1 in any of the 25 MBLR runs.

The validation of the model across 25 MBLR runs shows that the adjusted EBOR results are consistent and stable regardless of the choices of covariates and of the issues selected to borrow strength included in the model. The results remain stable regardless of the number of cefepime or comparator issues selected to borrow strength, and regardless of selecting the population of the 7 comparative FN studies or the 9 FN comparative and non-comparative studies (7 comparative, and 2 non-comparative).

We obtain the widest confidence when we select to analyze 14 covariates. We obtain the narrowest confidence limits when we reduce the number of covariates from 14 to 7 or less.

Yahav's FN paper and our review included studies ai411131, ai411186, ai411189, ai411198, and ai411204 (the study with the highest proportion of cefepime deaths). Yahav did not have access to studies ai411118 and ai411137, and did not assess the two non-comparative studies ai411143 and ai411158 (See Table 1 for the characteristics of the studies we analyzed).

It is important to note that Yahav, et al had access to secondary, published data, but not to the raw data that we used to analyze the data in-house. These authors seem to have analyzed the treatment of the first episode of FN (4), while we analyzed the treatment of the most recent episode of FN, closer to the death outcome. These authors used a fixed effects model in their statistical analysis that *did not* adjust for multiplicity and small counts by borrowing strength from other issues.

The independent FDA meta-analysis by Dr. Yu-te Wu dated January 14, 2009, assessed other indications beside FN that were not available in SDTM CDISC standards. Her analysis has the characteristics of a fixed effect model weighted by the proportion of patients in each study. Like our analysis, Yu-te Wu analyzed the treatment of the most recent episode of FN. Unlike our analyses, Wu did not adjust for multiplicity and small counts by borrowing strength from other issues.

In her review, Yu-te Wu found that the overall mortality risk difference in the cefepime group was greater than the comparator, but that the difference was not statistically significant.

Our overall unadjusted analysis shows a similar non-statistically significant effect as Yu-te Wu's analysis. However, the effect becomes closer to 1 when we adjusted by borrowing strength.

Yu-te Wu's subgroup analysis of medical history of Solid Tumors (ST) that *was not* adjusted for multiplicity showed a significantly greater mortality, but with wide CIs that overlapped the CIs for the overall estimate. Wu concluded that there is a need to re-examine her results when more data are available because of the small numbers behind this estimate.

In our unadjusted analysis, when ST is in the model, unadjusted OR>1 estimates occur when Studies + Age + Race + AL (medical history of acute leukemia) are also included in the model. This effect is seen with or without the addition of BMT (concomitant medication for Bone Marrow Transplant) or BMT + NEU (baseline neutropenia <=100), but not with fewer or more covariates in the model.

The unadjusted results are definitively borderline results. The unadjusted estimates are subject to the multiple comparison issues. One such example is our finding of an OR05>1 for the age category <=60 years, not detected in the age category >60 years in any of the 25 MBLR runs. This finding is not consistent with biological plausibility.

The unadjusted results could be false positive results. The unadjusted confidence limits are larger, more unstable, less precise, and wider than the adjusted ones. Every CI for the overall OR estimate included 1. Each of the covariate-defined subgroups had CI's for OR values that overlapped the CI's for overall OR values and in general included 1.

In any given situation, narrower and more stable confidence intervals can make a big difference in the quality and in the results obtained. This is especially important in the area of CT drug safety analysis, whereas the problem with small counts and multiple comparisons issues are very significant.

The Agency can expect an increase in publications/citizen petitions based on meta-analyses of public domain CT results. It is also often necessary to reanalyze CT data in light of new information about a particular adverse event or class of events for a drug or class of drugs months—or even years—after the initial analysis. With current ad-hoc methods, the prevalent use of non-standardized data and lack of automated review tools, the process of re-evaluation may take as long to perform as the original review.(5)

In many such situations, the Center will benefit from having ready access to standardized CT data and to standardized automated analytical tools.

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Tables

2. Acronyms, abbreviations, and terms used interchangeably

AD   PT: Abdominal distension (COMP Issue)

AL   Medical History of Acute Leukemia (Covariate)

AMM   Concomitant anti-microbial medication

Adjusted result   Empirical Bayesian adjusted result. Improved estimate generated by modeling and shrinkage. "Adjusted" denotes estimates from a model that includes multiple predictors whose effects have been "adjusted" by borrowing strength from the estimates of other response analyses.

Automated screening	Analyses include pre-programmed MedDRA PT, HLT, HLGT, and SOC Analyses, Standardized MedDRA Query Analysis, Custom MedDRA Query Analysis, QT Interval Prolongation Analysis, Subject Disposition Analysis, Clinically Significant Lab Analysis, Lab Change from Baseline Analysis, Hy's Law Analysis, Clinically Significant Vitals Analysis, Vitals Change from Baseline Analysis
BD	SMQ: Biliary disorders (SMQ) [narrow] (COMP Issue)
BMS	Bristol-Meyers Squibb
BMT	Concomitant Medication for Bone Marrow Transplant (Covariate)
C-only	Comparator-only estimates
CARS	"Computer Assisted Review of Safety" Committee chaired by Dr. Robert Temple in 1996
CEF	Cefepime arm
CHC	HLT: Central nervous system haemorrhages and cerebrovascular accidents (CEF Issue)
CI	Confidence Interval
CM	Concomitant medication
CNSH	SMQ: CNS haemorrhages and cerebrovascular accidents [narrow] (CEF Issue)
COMP	Comparator arm
CT	Clinical Trial
CTSD	Automated Clinical Trials Signal Detection software
CVD	SMQ: Cerebrovascular disorders [narrow] (CEF Issue)
Cluster Miner	Process that identifies clusters (or sets) of issues (for example, death, cerebral bleeding) that co-occur under treatment more often than the occurrence rates for the component individual issues under treatment would lead one to expect; cluster mining is based on a comparison of Empirical Bayesian adjusted odds ratio statistics for issue pairs and the treatment drug [6]
Covariate	Covariate, predictor, or subgroup considered medically important to study in the logistic regression run including, treatment and interactions with treatment, studies, subject characteristics, concomitant medications or conditions, and baseline laboratory values or vitals
Creatinine	Serum creatinine values
DAIOP	Division of Anti-Infective and Ophthalmology Products
DCRP	Division of Cardiovascular and Renal Products

Death (PT)	Custom PT term named 'Death' created to include in a single place all the deaths assessed by Dr. Peter Kim as evaluable deaths. This custom term was generated to address the lack of a unique placeholder for all categories of 'Death' in the SDTM CDISC standards, or in the data submitted using traditional formats
EOT	End of treatment
FN LE	Febrile neutropenia, last (most recent) episode (and treatment allocation) relative to death
FN	Febrile Neutropenia
HCC	SMQ: Haemorrhagic cerebrovascular conditions [narrow] (CEF Issue)
HLT	MedDRA High Level Term
HT	PT: Hypertension (COMP Issue)
Hierarchical Bayesian model	Could be reformulated as a non-Bayesian random effects model, where the response-by-predictor interaction terms would be viewed as random effects
Issue	In the MBLR run, issues are the adverse event or medically related adverse events used to borrow strength to compute the Bayesian or adjusted OR (for example, death, cerebral bleeding). MBLR uses exactly the same predictors to compute the response to every issue selected in an MBLR run. To compute unadjusted OR, the borrowing strength from issues does not take place.
Indication in MBLR	Study (reviewer used study instead of an indication breakdown)
J	PT: Jaundice (COMP Issue)
K-M survival curves	Kaplan-Meier survival curves
LE	Last episode of febrile neutropenia (FN) and treatment allocation relative to death
LR	Logistic Regression
Loading and checking run	Batch run that loads study data and checks for compliance with SDTM CDISC
MBLR	Multivariate Bayesian Logistic Regression, a statistical analysis component of the automated CTSD software within the WebSDM electronic data submission platform
MH	Medical history
MO	Medical Officer
MedDRA	Medical Dictionary for Regulatory Activities developed by the International Conference on Harmonization (ICH)

Multivariate	Refers to the fact that the MBLR method considers multiple responses together, at once
N	No (For example, Acute leukemia:N = no Acute leukemia)
NEU	Baseline Neutropenia covariate
NM display	"Napoleon's March" display
PP	Patient Profile Data software—Interactive Graphical Display of Patient Data
Pooled studies	Study obtained by combining studies
Predictor	Predictor, covariate, or subgroup considered medically important to study in the logistic regression run including, treatment and interactions with treatment, studies, subject characteristics, concomitant medications or conditions, and baseline laboratory values or vitals
PT	Preferred Term of the MedDRA terminology
R	PT: Rales (COMP Issue)
Reducing uncertainties	Reducing false positive signals and increasing true positive ones
Response	The results to all covariates (all subgroups considered important to study as predictors) that may be associated with a specific issue (for example, death) or with compound issues (for example, death, cerebral bleeding) used to borrow strength. MBLR uses exactly the same predictors for each response to an issue in an MBLR run.
Run	Implies an MBLR run
SDTM CDISC	Study Data Tabulation Model (SDTM) of the Clinical Data Interchange Standards Consortium (CDISC)
SMQ	Special MedDRA Queries
SOR	Syndromic Odds Ratio
ST	Medical history of Solid Tumor (Covariate)
Screening Analysis	This process generates in an automated fashion a set of statistical analyses for associations of a treatment group (as compared to a comparator group) and different types of events by demographic groups potentially affected. For example, for a MedDRA PT disproportionality analysis, the issue is a particular adverse event Preferred Term (PT) and the statistics is a "shrunken odds ratio; for changes from Baseline in Labs and Vitals the statistics are p values
	The following steps are part of screening analysis: The user creates a screening analysis specification by: specifying treatment and comparator groups; defining subgroups of subjects based on such factors as sex, race, age, medical history, concomitant medications; and studies. The user then includes one or multiple analysis types, such as a MedDRA PT

Analysis and a Clinically Significant Lab Analysis, in the analysis specification

Screening Run	In this review, it implies the run generated using Shrunken OR by MedDRA PT
Study pool	Study data obtained by combining several studies
Subgroup	Subgroup, covariate, or predictor considered medically important to study in the logistic regression run including, treatment and interactions with treatment, studies, subject characteristics, concomitant medications or conditions, and baseline laboratory values or vitals
Supplemental qualifier	SDTM-compliant variables that capture values for which there are no standard variables in the general observation classes
T-C	Treatment-Comparator estimates
TT	The TableTrans software, a visual programming environment for large-scale data manipulation
Unadjusted result	Standard logistic regression result. "Unadjusted" denotes results from standard logistic regression analyses using one response at a time
VHD	HLT: Vascular hypotensive disorders (CEF Issue)
WebSDM CTSD	Web Submission Data Manager (WebSDM) platform that integrates data from clinical trials into a SDTM CDISC -compliant data repository and performs automated screening for potential safety issues using the automated Clinical Trials Signal Detection (CTSD) software
Y	Yes (For example, Acute leukemia:Y = Acute leukemia present)

A graph for EB results shows confidence interval lines representing the following:

EBOR	Empirical Bayesian Odds Ratio
EBOR05	A value such that there is approximately a 5% probability that the true Odds Ratio lies below it
EBOR95	A value such that there is approximately a 5% probability that the true Odds Ratio lies above it

A graph for unadjusted results shows confidence interval lines representing the following:

OR	Odds Ratio
OR05	A value such that there is approximately a 5% probability that the true Odds Ratio lies below it
OR95	A value such that there is approximately a 5% probability that the true Odds Ratio lies above it

Note to the Reader:

For the sets of MBLR output figures generated directly by the WebSDM CTSD software, we could not select to display in a common scale the estimates for adjusted and unadjusted T-C results (see example in Figure 6) and C only values (see example in Figure 5). Therefore, the reader needs to interpret the MBLR graphic displays by focusing first on the scales below each minigraph.

3. Medical Officer's Consult Review

3.1. *Introduction*

The Division of Anti-Infective and Ophthalmology Products officially requested Dr. Szarfman's help in trying to understand a reported as statistically significant mortality imbalance with cefepime and FN in two meta-analyses by Paul, Yahav et al and by Yahav, Paul et al.(1,2).The marketed drug cefepime is a mainstay therapy for patients with fever and neutropenia.

Dr. Peter Kim also asked Dr. Szarfman to aid in the identification of all patients who died in the trials, and to help support his MO review.

To address this consult request, this reviewer implemented a functional prototype of a novel Multivariate Bayesian Logistic Regression (MBLR) data mining method developed by Dr. William DuMouchel.

MBLR is an enhanced form of pooled-data meta-analysis. MBLR performs pooled-data meta-analysis of complete subject level data in the SDTM CDISC format. This method corrects for multiplicity and small counts, and improves the signal to noise ratio. This correction is important for reducing false discoveries in CT safety data.

This novel prototype embedded within the WebSDM CTSD software (7) was implemented under Requisition #1047767.

3.2. *Methods*

3.2.1. *Episode of Febrile Neutropenia Analyzed*

As described before in this review, if more than one episode of FN occurred, we analyzed the study drug assigned to each patient during the most recent episode of FN relative to death, and the baseline for the corresponding first day of the most recent episode of FN. We named this type of analysis "Last episode of FN" or "Most recent episode of FN" relative to death. In this report, we use these terms interchangeably.

3.2.2. *Febrile Neutropenia Studies*

We analyzed 30-day all cause mortality and potential covariate-defined subgroups at risk in the 9 FN studies submitted by the applicant in SDTM CDISC standards.

Two of the 9 studies were uncontrolled. Of the 7 controlled studies, 3 compared cefepime to ceftazidime, 2 compared cefepime to combination therapy, and 2 compared cefepime in combination to combination therapy as detailed in Table 1.

These 9 studies were mostly small studies. Five (5) of the 9 studies enrolled less than 120 patients per study)

Taking into account the 1:1 randomization of study ai411131 and the 2:1 randomization of study ai411186, these studies had 14 (15.6%) and 20 (9%) more patients, respectively in the cefepime arm than expected by the enrollment numbers in the comparator arm. Not such high disproportion with comparator patients was seen in other studies. Study ai411186 was an acute leukemia (AL) study. The AL patients are expected to have a higher acute risk of death than ST patients (Table 1)

The small size of the studies made them vulnerable to the problem of small counts and multiple comparisons issues.

The multiple episodes of FN and re-randomization of patients made these studies vulnerable to an unbalanced number of treatment-comparator patients.

Indeed, the cefepime patients seem to have been sicker *at baseline*. There were 6.25% additional cefepime patients with AL *or* bone marrow transplant (BMT) at baseline. These covariates are associated with acute risk of death. They included 61.7% on cefepime (549/890) and 55.4% on comparator (347/626).

These studies had 9.1% additional cefepime patients who **_did not receive_** concomitant antimicrobial medication (AMM). They included 48% on cefepime (428/890)] and 39% on the comparator (244/626)].

Table 1: Study characteristics in the last episode of FN

Study	Cefepime		Comparator		Total
	N	%	N	%	N
CS ai411118 Cefepime* vs Piperacillin + Gentamicin 1:1 Phase III, AC Comb, Open Randomized, USA (one episode of FN, no treatment allocation change)	59	50.86	57	49.14	116
CS ai411131 Cefepime* vs Ceftazidime*** 1:1 Phase III, AC, Open Randomized, USA (up to 5 episodes of FN [ended up with a total of 10 more cefepime patients in the last episode of FN than in the first])****	104	53.61	90	46.39	194
CS ai411137 Cefepime* vs Mezlocillin + Gentamicin 1:1 Phase III, AC Comb, Open Randomized, USA (one episode of FN, no treatment allocation change)	35	49.3	36	50.7	71
CS ai411186 Cefepime** + Amikacin vs Ceftazidime*** + Amikacin 2:1 Phase III, AC Comb, Open Randomized, France (one episode of FN)****	242	68.56	111	31.44	353
CS ai411189 Cefepime* vs Ceftazidime*** 1:1 Phase III, AC, Open Randomized, Multi-country, Non-USA (up to 5 episodes of FN, [ended up with a total of 5 more cefepime patients in the last episode of FN than in the first])	144	51.25	137	48.75	281
CS ai411198 Cefepime* + Vanconycin vs Ceftazidime*** + Vancomycin 1:1 Phase III, AC Comb, Open Randomized, Belgium (up to 3 episodes of FN [ended up with a total of 1 more cefepime patient in the last episode of FN than in the first])	54	48.65	57	51.35	111
CS ai411204 AC Cefepime* vs Ceftazidime*** 1:1 Phase III, AC, Double-blind Randomized, USA (up to 5 episodes of FN, [ended up with a total of 5 more cetazidime patients in the last episode of FN than in the first])	138	50	138	50	276
NC ai411143 Cefepime* Uncontrolled Phase II, Open, Belgium, Switzerland (pts changed start date)	84	100	0		84
NC ai411158 Cefepime* Uncontrolled Phase II, Open, Netherland (one episode of FN, no treatment allocation change)	30	100	0		30
Total 7 Comparative Studies, [ended up with a total of 11 more cefepime patients in the last episode of FN than in the first]	776	55.35	626	44.65	1402
Total 9 Comparative and Non-comparative Studies [ended up with a total of 11 more cefepime patients in the last episode of FN than in the first]	890	58.71	626	41.29	1516

Study design: AC: Active Controlled, Comb: Combination therapy, Uncontrolled
* Cefepime 2g q8h
** Cefepime 2g q12h
*** Ceftazidime 2g q8h
**** Studies ai411131 and ai411186 enrolled 15.6% and 9% more patients than what it was expected for each of these studies, respectively. Taking into account the 1:1 randomization of study ai411131, this study enrolled 104 patients in the cefepime arm, 15 more than in the comparator arm. Taking into account the 2:1 randomization of study ai411186, we expected only 222 cefepime patients, but the study enrolled 242, in the cefepime arm, 20 more patients than in the comparator arm. Not such disproportion was seen with the comparators in other studies.
Seven of the 9 studies were active controlled, and 2 uncontrolled.

Of the 7 controlled studies, 3 compared cefepime to ceftazidime (studies ai411131, ai411189, and ai411204), 2 compared cefepime to combination therapy (studies ai411118 and ai11137), and 2 compared cefepime in combination to combination therapy (ai11186 and ai11198).

Only Study ai411204 was both, a double-blinded and randomized study.

3.2.3. *Distribution of Deaths*

As described in Dr. Peter Kim's Medical Officer review dated January 20, 2009 and amended on April 4, 2009, to analyze the reported mortality imbalance we needed first to find all the evaluable deaths.

The 30-day all-cause mortality rate for cefepime in the 9 FN studies (comparative and non-comparative) was 8.2% (73/890), and in the 7 comparative ones 7.87% (61/776). For the comparator arms of the 7 and 9 FN studies, this rate was 6.6% (41/626). In the 3 comparative studies vs ceftazidime, the cefepime death rate was 9.84% (38/386) and the ceftazidime was 7.95% (29/365) (Table 2).

The comparative study with the highest percentage of cefepime deaths was Study ai411204 (15% [21/138] for cefepime and 10% [13/138] for ceftazidime) followed by study ai411131 (10% [9/104] for cefepime and 7.7% [6/90] for ceftazidime) and by study ai411198 (9.5% [5/54] for cefepime + vancomycin and 5.2% [3/57] for ceftazidime + vancomycin).

The comparative study with the highest percentage of comparator deaths was Study ai411189 (5.56% [8/144] for cefepime vs. 7.3% [10/137] for cetazidime).

Within the uncontrolled studies Study ai411158 had a 13.3% [4/30] of cefepime deaths and study ai411143 9.5% [8/84] of cefepime deaths.

Table 2: Distribution of evaluable deaths by study and by treatment arm in the last episode of FN

	Deaths						Total number of patients		
	Cefepime		Comparator		Total		Cefepime	Comparator	Total
Studies	N	%	N	%	N	%	N	N	
CS ai411118 Cefepime* vs Piperacillin + Gentamicin 1:1	5	8.47	4	7.02	9	7.76	59	57	116
CS ai411131 Cefepime* vs Ceftazidime 1:1	9	8.65	6	6.67	15	7.73	104	90	194
CS ai411137 Cefepime* vs Mezlocillin + Gentamicin 1:1	0	0.00	1	2.78	1	1.41	35	36	71
CS ai411186 Cefepime + Amikacin vs Ceftazidime + Amikacin 2:1	13	5.37	4	3.60	17	4.82	242	111	353
CS ai411189 Cefepime vs Ceftazidime 1:1	8	5.56	10	7.30	18	6.41	144	137	281
CS ai411198 Cefepime* + Vanconycin vs Ceftazidime + Vancomycin 1:1	5	9.26	3	5.26	8	7.21	54	57	111
CS ai411204 AC Cefepime vs Ceftazidime 1:1	21	15.22	13	9.42	34	12.32	138	138	276
NC ai411143 Cefepime* Uncontrolled	8	9.52	0		8	9.52	84	0	84
NC ai411158 Cefepime* Uncontrolled	4	13.33	0		4	13.33	30	0	30
Total: 3 Cefepime vs Ceftazidime	38	9.84	29	7.95	67	8.92	386	365	751
Total: 7 Comparative Studies	61	7.86	41	6.55	102	7.28	776	626	1402
Total 9 Comparative and Non-comparative Studies	73	8.20	41	6.55	114	7.52	890	626	1516

Of the patients with AL *or* BMT at baseline, 58 died, 41 on cefepime [4.6% (41/890)] and 17 [2.7% (17/626)] on comparator.

Of the patients who ***did not receive*** concomitant antimicrobial medication (AMM) 44 died, 33 on cefepime [3.71% (33/890)], and 11 [1.76% (11/626)] on comparator.

3.2.4. *Timing of Death*

We assessed the timing of these deaths since the beginning of the most recent episode of FN. If only one episode of FN occurred, we analyzed the timing of death for the first episode of FN.

Overall, the median survival across all 9 studies was similar: 20 days for cefepime and 18 days for the comparator (Figure 25). However, cefepime deaths tended to occur earlier in the beginning of the treatment or later than comparators in the end of the observation period (page 80).

In study ai411204, the study with the highest proportion of cefepime deaths, median survival was 22 days for cefepime and 12 days for the comparator (Figure 26).

We could not study the relationship between the degree of neutropenia prior to death and death because the sponsor stopped collecting neutrophil counts after EOT (Figure 36).

3.2.5. *The Automated Analysis Environment*

The WebSDM CTSD Analysis Environment:

- Forces the use of standardized data in the SDTM CDISC format (8)

- Checks and identifies data errors and inconsistencies early in the review process

- This environment enables the creation of a full set of validated, centrally programmed, very precise and automated analytical outputs

    o The analytical outputs and the raw data tables are hyperlinked to more details in the data, including to Patient Profiles

    o This enables a better comprehension of the multivariate data being analyzed, as well as confirmation that the data transformation processes that were used were indeed correct

- These functions also increase the ability of the reviewer to identify and document data problems that require correction, to make (or to request) informed data corrections, and to rerun the analyses with updated and corrected information in real time

- An important point is that the loaded data sets are "read only" to protect them from corruption during the review process

3.2.5.1. *Steps Required to Automate the Analytical Process*

- Loading the data in a common Study Data Tabulation Model (SDTM) format for each study into Web Submission Data Manager (WebSDM)

- Reviewing the data error logs as well as the hyperlinked interactive graphic and tabular displays of the data automatically generated by WebSDM CTSD

- Correcting several data problems that are roadblocks for the automated analysis

- Producing study pools (study data obtained from combining studies)

- Selecting study pools of interest

- Reviewing the hyperlinked interactive graphic and tabular displays of the data automatically generated by WebSDM CTSD

- Selecting screening strategies from a menu of already programmed statistical methods such as Shrunken OR, p values and graphic displays such as Sector Maps, Napoleon's March, etc

- Generating issue clusters by using the Cluster Miner

  o [Cluster Mining is a process that identifies clusters (or sets) of issues (for example, death, cerebral bleeding) that co-occur under treatment more often than the occurrence rates for the component individual issues under treatment would lead one to expect; cluster mining is based on a comparison of Empirical Bayesian adjusted odds ratio statistics for issue pairs and the treatment drug] (6)]

- Selecting as many covariates and issues as needed, and generate the MBLR runs from a menu

- Reviewing the results

- Selecting from a menu the predictors that could make a difference in the MBLR model (the ones showing the most non-overlapping results within the comparator arm)

- Reviewing the additional MBLR results

3.2.5.2.   *Data Submitted for Analysis*

To perform the cefepime review using MBLR and other automated analytical tools, we requested the data to arrive in SDTM CDISC standard format (8). The data for 9 FN studies arrived in this format. The standard format enabled us to automatically and rapidly load the data for the 9 studies into the WebSDM CTSD software (7).

3.2.5.3.   *Problems with the Data Submitted, and how they were Addressed*

As described in Dr. Peter Kim's Medical Officer review, to analyze the reported mortality imbalance we needed first to find all the evaluable deaths.

After 11 years of trying to build data standards for CT data, there is still not a unique place for all categories of 'Death' in the SDTM CDISC standards, nor in the data submitted using traditional formats. Note that 'Death' is a key data element for this review, and for the review of any NDA.

To expedite a solution for this review, we created a new and unique Preferred Term (PT) in the data named 'Death' that included in a single place all the deaths that were assessed by Peter Kim as evaluable deaths. For a more global solution applicable to other types of CTs we suggested a solution to the CDIC organization (see Section 4.18 of the appendices.)

We also addressed other data barriers for the automated analysis regardless of being or not being SDTM CDISC standards problems, described in Section 4.5.3 below of the appendices.

3.2.5.4.   *Date of the Data Load Used for this Review*

For this review, we used the data we corrected and loaded into WebSDM CTSD on February 6, 2009.

3.2.6. *Analyses Performed Using other Software Packages*

We used the Patient Profile software to perform more detailed Survival Analyses and Napoleon's March Graphs displays for several covariates and for the relationship between the timing of severe neutropenia

and death, and described these analyses in section 4.12.2 below entitled "Napoleon's March" Displays"
and section 4.12.1 below entitled Kaplan-Meier Survival Curves." We also used the Table Trans and
Patient Profile software to integrate the data across 25 independent MBLR runs and to display the values
for these runs in Figure 21 and Figure 22 and similar figures in the appendices (starting on page 97 and
page 140).

3.2.7. *The MBLR Data Mining Method*

- MBLR stands for Multivariate Bayesian Logistic Regression.(9)

- MBLR is a part of a set of centrally programmed interactive analytical tools and graphic displays
  within the WebSDM CTSD software.

- As the other programs in WebSDM CTSD, it requires complete subject level data in a common
  SDTM CDISC format.

- A common SDTM CDISC format facilitates data pooling across studies.

- MBLR performs pooled-data meta-analysis of complete subject level data in the SDTM CDISC
  format.

- The combined analysis of multiple studies using MBLR, a method that corrects for multiplicity and
  small counts, is an enhanced form of pooled-data meta-analysis.

- MBLR currently estimates adjusted responses across two or more issues at once.

- For the experimental run whereas MBLR estimates the response to one issue the MBLR looks at
  all the covariates, shrinking them toward the null hypothesis of a EBOR of 1 (not shown).

3.2.7.1. *MBLR in Plain English*

In plain English, the MBLR estimates would be similar to the "weighted average of the subgroup effect and
the overall effect" described in a recent article by Dr. Janet Wittes (3).

MBLR also addresses the task of analyzing multiple responses and multiple covariates at once, and uses
shrinkage to help prevent false positives.

MBLR performs at once, pooled data assessments over multiple studies and multiple covariates
considered medically important and over multiple medically related events, and corrects for multiplicity and
small counts.

This hierarchical Bayesian model could be reformulated as a non-Bayesian random effects model, where
the response-by-predictor interaction terms would be viewed as random effects.

3.2.7.2. *What does 'Multivariate' refer to?*

Multivariate refers to the fact that the method considers multiple responses together, including:

1. All the covariates (or subgroups at risk) considered medically important (rows in Figure 1),

2. One or multiple issues (or medically related adverse events (for example, death, cerebral bleeding))
considered important (pages in Figure 1).

For every non-treatment predictor in the model (the comparator only, shown in the top half of Figure 1) the treatment interaction with that predictor (shown in the bottom half of Figure) is automatically included in the model.

For the responses being analyzed in an MBLR run (for example, death, cerebral bleeding, pages in Figure 1), the estimates of the response analysis to each one of the medically related adverse event (for example, death) "borrows strength" from the estimates of the other response analyses (for example, cerebral bleeding).

If the estimates across responses are in close statistical agreement, the borrowing strength aspect of the Bayesian regressions can provide additional power compared to the separate non-Bayesian regressions that do not borrow strength. On the other hand, if these estimates differ significantly, the shrinkage towards 0 (zero) will provide conservative effect estimates that can be interpreted as an adjustment for multiple comparisons (9).

For every non-treatment predictor in the model (the comparator only, shown on the top half of Figure 1), the treatment-comparator interaction with that predictor (shown on the bottom half of Figure 1) is automatically included in the model.

Figure 1: What does 'multivariate' refer to? (in color)
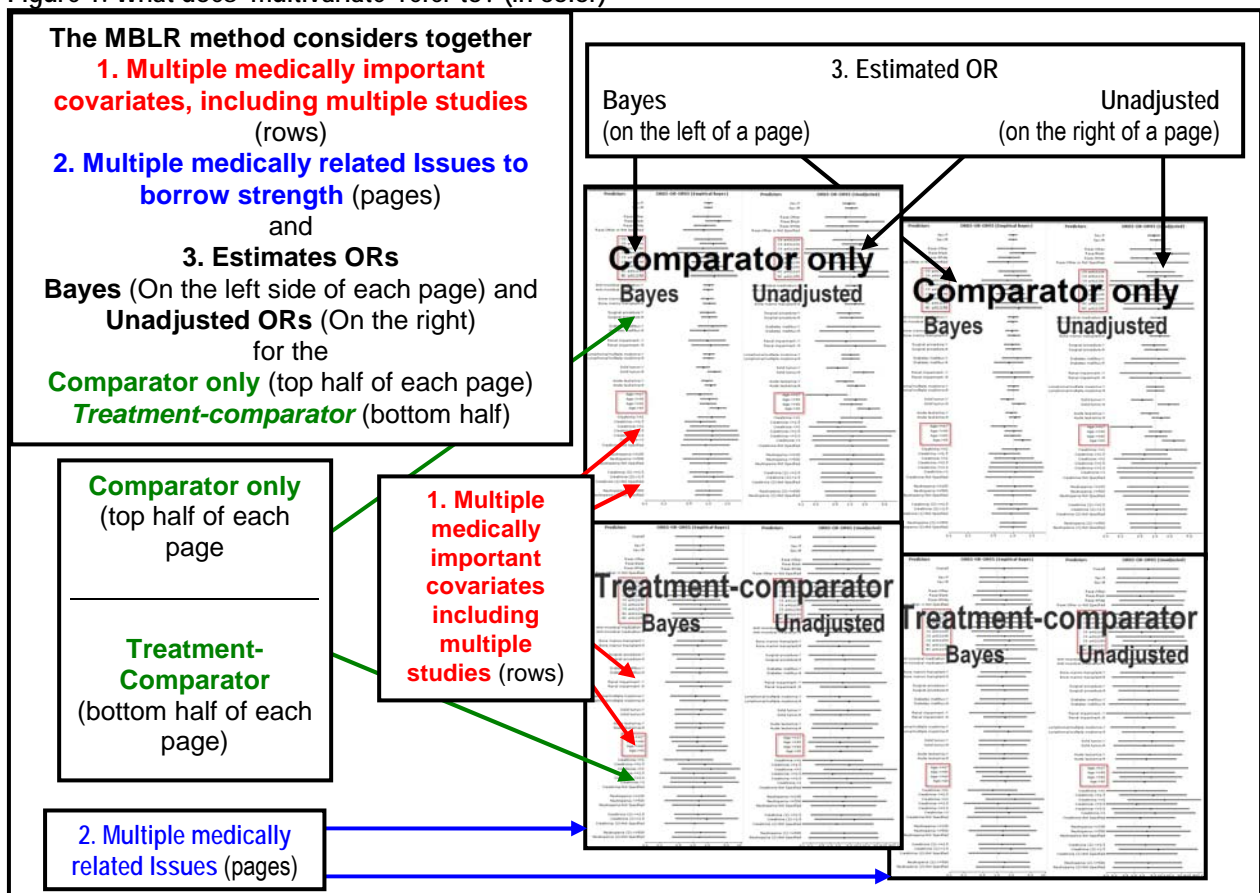
3.2.7.3. *How does MBLR Reduce Uncertainties about Safety Outcomes?*

- The MBLR method corrects for multiplicity and for small counts.

- The modeling and shrinkage in the MBLR method help prevent false positives and improve the generation of true positives.

- The MBLR method adjusts unstable estimates by shrinkage, and shrinks the most unstable, volatile estimates the most.

- It generates tighter confidence intervals (also known as credible estimates) for responses to as many covariates (also known as subgroups or predictors) and studies as considered clinically necessary, and to as many medically related outcomes as needed, at once.

3.2.8. *'Death' Assessment using MBLR*

We studied the deaths occurring up to 30-days following the end of the last treatment exposure in the 9 FN studies.

We studied the effect of 'Death' by first using in the MBLR model as many covariates as considered medically necessary (See list of the 14 covariates initially selected for analysis in Table 3).

Table 3: List of the 14 covariates considered medically important assessed in the MBLR analysis runs

• Treatment arms (most recent episode of FN)	• Medical history (most recent episode of FN):
• Age (several cut-points)	– Diabetes mellitus (yes/no)
• Sex (F/M)	– Renal impairment (yes/no)
• Race (several categories)	– Lymphoma/multiple myeloma (yes/no)
• 9 studies (7 controlled, and 2 uncontrolled)	– Solid tumor (yes/no)
• Concomitant Medications:	– Acute leukemia (yes/no)
– Antimicrobial medication (yes/no)	• Baseline labs (most recent episode of FN):
– Bone marrow transplant (yes/no)	– Creatinine (2) (several cut-points)
– Surgical procedure (yes/no)	– Neutropenia (3) (several cut-points)

To borrow strength, we used in the MBLR analysis a number of issues associated with Death in the cefepime (CEF) arm, and a number of issues associated with Death in the comparator (COMP) arm (Table 7)

For example, the MBLR run 923 included the 14 covariates listed in Table 3 that we selected as medically plausible predictors of cefepime deaths and the 6 CEF issues (including 'Death') listed in Table 8 that we used to borrow strength.

For this run with 14 covariates, MBLR generates at once 190 OR values for each one of the 6 issues used to borrow strength (85 adjusted OR values for the comparator only and for the treatment-comparator and the same number for the corresponding 85 unadjusted OR values).

3.2.8.1. *Example of One of the 25 MBLR Performed: Outputs from Run 923*

Figure 2: Audit trail of the configuration used in run 923 (run included 9 studies [not shown])

Configuration options for the selected BLR run:

Dosing

Arm of last randomization {Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime'; Comparator includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';}

Predictors

Age:
  Age {<=17 <= 17.0; 17.0 < <=40 <= 40.0; 40.0 < <=60 <= 60.0; 60.0 < >60;}

Sex:
  Sex {F includes: 'F'; M includes: 'M';}

Race:
  Race {Other includes: 'H', 'O', 'X'; Black includes: 'B'; White includes: 'W';}

Concomitant Medications:
  Anti-microbial medication {Antimicrobial medication includes: 'Concomitant Antimicrobial Medication', 'Post Study Antimicrobial Therapy';}
  Bone marrow transplant {Bone marrow transplant includes: 'Bone Marrow Transplant';}
  Surgical procedure {Surgical procedure includes: 'Concomitant/Post Therapy Surgical Procedures';}

Medical History:
  Diabetes mellitus {Diabetes mellitus includes: 'DIABETES MELLITUS', 'Other: GLUCIDIC INTOLERANCE DIAGNOSED';}
  Renal impairment {Renal impairment includes: 'Other: LOW GRADE RENAL INSUFFICIENCY', 'Other: IMPAIRED KIDNEY FUNCTION', 'Other: NON-FUNC L/KIDNEY';}
  Lymphoma/multiple myeloma {Key MHs includes: 'MALIGNANT LYMPHOMAS', 'NON-HODG LYMPHOMA,MULT MYELOMA', 'Other: CHEMOTHERAPY FOR MALIGNANT LYM', 'MULTIPLE MYELOMA', 'MDS + MULTIPLE MYELOMA';}
  Solid tumor {Solid tumor includes: 'ALIMENTARY TRACT CANCER', 'BREAST CANCER', 'CANCER OF ENDOCRINE GLANDS', 'CANCER OF UNKNOWN ORIGIN', 'LUNG CANCER', 'MALE GENITAL CANCER', 'Other: CANCER PAIN', 'Other: CHRONIC CANCER PAIN', 'UROLOGIC CANCER', 'BONE TUMORS', 'CENTRAL NERVOUS SYSTEM TUMORS', 'HEAD AND NECK TUMORS', 'Other: SOLID TUMOR OF THE RENAL PAREN', 'Other: YOLK SAC TUMOR', 'TUMORS OF FEMALE REPR.ORGANS', 'TUMORS OF THE EYE', 'MALIGNANT MELANOMA', 'NEUROBLASTOMA', 'Other: NEUROBLASTOMA', 'SOFT TISSUE SARCOMA', 'Other: ADENOCARCINOMA OF UNKNOWN PRIM', 'Other: SQ CELL CARCINOMA ANAL CANAL', 'UNDIFFERENTIATED CARCINOMA (ME', 'Other: METASTATIC LESION BEHIND RIGHT', 'CA OF MAJOR DIGESTIVE GLANDS', 'Other: NEOPLASTIC DISEASE';}
  Acute leukemia {Acute leukemia includes: '10.92 ACUTE MYELOID LEUKEMIA', '5.12.92 ACUTE MYELOID LEUKEMIA', 'ACUTE BIPHENOTYPIC LEUKAEMIA', 'ACUTE MEYLOID LEUKAEMIA', 'ACUTE MYCLOBLASTIC LEUKEMIA M1', 'ACUTE MYCLOID LEUKEMIA', 'ACUTE MYELOBLASTIC LEUCEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA M1', 'ACUTE MYELOBLASTIC LEUKEMIA M5', 'ACUTE MYELOGENOUS LEUKAEMIA', 'ACUTE MYELOGENOUS LEUKEMIA M2', 'ACUTE MYELOGENSUS LEUKAEMIA', 'ACUTE MYELOIC LEUKAEMIA', 'ACUTE MYELOID LEUCAEMIA', 'ACUTE MYELOID LEUCEMIA (RABM3', 'ACUTE MYELOID LEUKAEMIA', 'ACUTE MYELOID LEUKAEMIA (M1)', 'ACUTE MYELOID LEUKAEMIA (M7)', 'ACUTE MYELOID LEUKAEMIA - MI', 'ACUTE MYELOID LEUKAEMIA M5', 'ACUTE MYELOID LEUKEMIA', 'ACUTE MYELOID LEUKEMIA (AML M1', 'ACUTE MYELOID LEUKEMIA (HYPER', 'ACUTE MYELOID LEUKEMIA (M3)', 'ACUTE MYELOID LEUKEMIA (MX)', 'ACUTE MYELOID LEUKEMIA M2', 'ACUTE MYELOID LEUKEMIA SINCE 1', 'ACUTE MYELOID LEUKEMIA ST POST', 'ACUTE MYELOID LEUKEMIA,TYPE M5', 'ACUTE MYELOIDE LEUKEMIA', 'ACUTE MYLEOID LEUKAEMIA', 'ACUTE MYLOID LEUKEMIA', 'AML-ACUTE MYELOGENOUS WITH MONOCYTIC SUBTYPE', 'LMA NY/ACUTE MYELOID LEUKEMIA', 'MACUTE MYELOID LEUKEMIA VERY', 'MYLEODYSPLASTC DISORDER EVOLVING INTO ACUTE LEUKEMIA', 'RELAPSED ACUTE MYELOIDLEUCHEMI', 'AML', 'AML - M3', 'AML - M5', 'AML - M5A', 'AML - MSQ DIAGNOSED 11/92', 'AML AFTER MDS-RAC-T, NOW RELAP', 'AML DIAGNOSED 060593', 'AML DIAGNOSED 2/92,NOW 2ND REL', 'AML FAB M6', 'AML M1', 'AML M3', 'AML M4', 'AML M5', 'AML M5A', 'AML OF M4-M5SUBTYPE', 'AML RELAPSE', 'AML SEC TO MYELOPROEIFERATIVE', 'AML SINCE 7/92 AFTER MOS (TY', 'AML, TYPE PROMYELOID', 'AML-M2', 'AML-M2 WITH TRANSLOCATION', 'AML-M5A', 'AML-MS DIAGNOSED 1/93', 'AML-MSA', 'MDS-AML', 'RAEB-T -> AML', 'AC MYELOID LEUKEMIA', 'LEUKEMIA : ALL', 'LEUKEMIA : ANLL', 'BLASTIC TRANSFORM OF MYELODYSP', 'MYELODYSPLASTIC SYNDROME IN BL', 'ACUTATIVE OF CHRONIC MYELOMONO';}

Baseline Labs:
  Creatinine (2) {<=2.5 <= 2.5; 2.5 < >2.5;}
  Neutropenia (3) {<=100 <= 0.1; 0.1 < <=500 <= 0.5; 0.5 < >500;}

Issues

  HLT: Central nervous system haemorrhages and cerebrovascular accidents {MedDRA HLT Disproportionality (Central nervous system haemorrhages and cerebrovascular accidents)...}
  HLT: Vascular hypotensive disorders {MedDRA HLT Disproportionality (Vascular hypotensive disorders) - from Issue Cluster 'Cluster #1'}
  PT: Death {MedDRA PT Disproportionality (Death) - from Issue Cluster 'Cluster #34'}
  SMQ: Cerebrovascular disorders [narrow] {Standard MedDRA Query (SMQ) Disproportionality (Cerebrovascular disorders [narrow]) - from Issue ...}
  SMQ: CNS haemorrhages and cerebrovascular accidents [narrow] {Standard MedDRA Query (SMQ) Disproportionality (CNS haemorrhages and cerebrovascular accidents [n...]}
  SMQ: Haemorrhagic cerebrovascular conditions [narrow] {Standard MedDRA Query (SMQ) Disproportionality (Haemorrhagic cerebrovascular conditions [narrow])...}

Options

  Issues occurring any time

Figure 3: Display options for each issue in run 923

Figure 4: Overall estimates for all the issues in run 923

Table 4: Overall estimates for all the issues in run 923

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Central nervous system haemorrhages and cerebrovascular accidents					
Empirical Bayes	-1	Overall	0.465	1.259	3.405
Unadjusted	-1	Overall	0.007	0.391	22.731

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Vascular hypotensive disorders					
Empirical Bayes	-1	Overall	0.445	0.974	2.132
Unadjusted	-1	Overall	0.19	2.846	42.525
Death					
Empirical Bayes	-1	Overall	0.549	1.113	2.258
Unadjusted	-1	Overall	0.201	1.918	18.27
Cerebrovascular disorders [narrow]					
Empirical Bayes	-1	Overall	0.465	1.259	3.405
Unadjusted	-1	Overall	0.007	0.391	22.731
CNS haemorrhages and cerebrovascular accidents [narrow]					
Empirical Bayes	-1	Overall	0.465	1.259	3.405
Unadjusted	-1	Overall	0.007	0.391	22.731
Haemorrhagic cerebrovascular conditions [narrow]					
Empirical Bayes	-1	Overall	0.481	1.353	3.8
Unadjusted	-1	Overall	0.011	0.804	57.737

The OR values are displayed in two columns (Figure 5 and Figure 6), the Bayes or adjusted on the left and unadjusted on the right) (10).Figure 5 shows the values for the "comparator only" analysis and Figure 6 for "treatment-comparator" analysis. The corresponding counts and estimates are also shown in Table 4 and Table 5.

Figure 5: Adjusted (left column) and unadjusted (right column) effects of covariates within the comparator arm (Issue = 'Death', run 923)
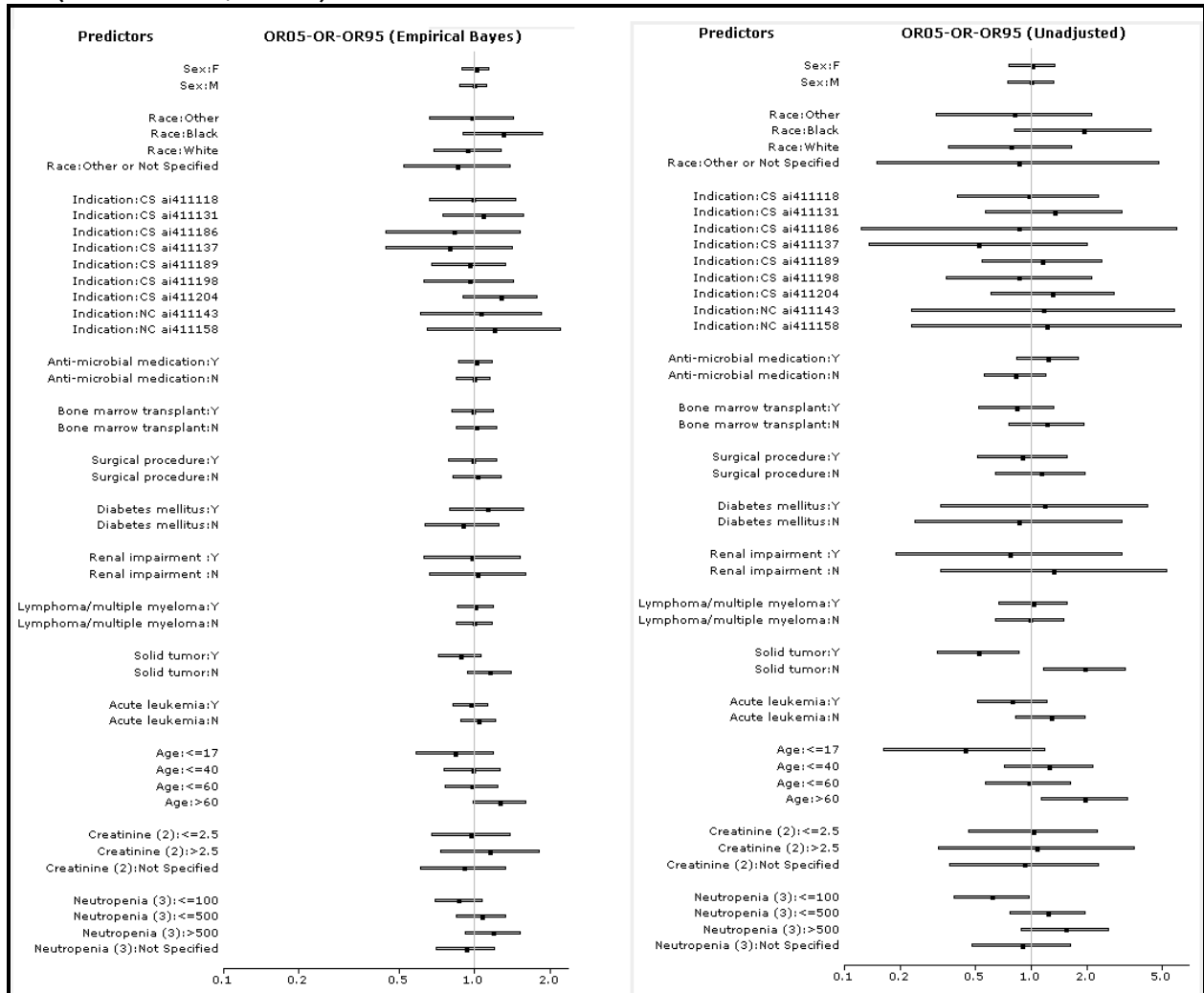
Figure 6: Adjusted (left column) and unadjusted (right column) treatment-comparator Odds Ratios, Overall and for Covariate Subgroups (Issue = 'Death', Run 923)
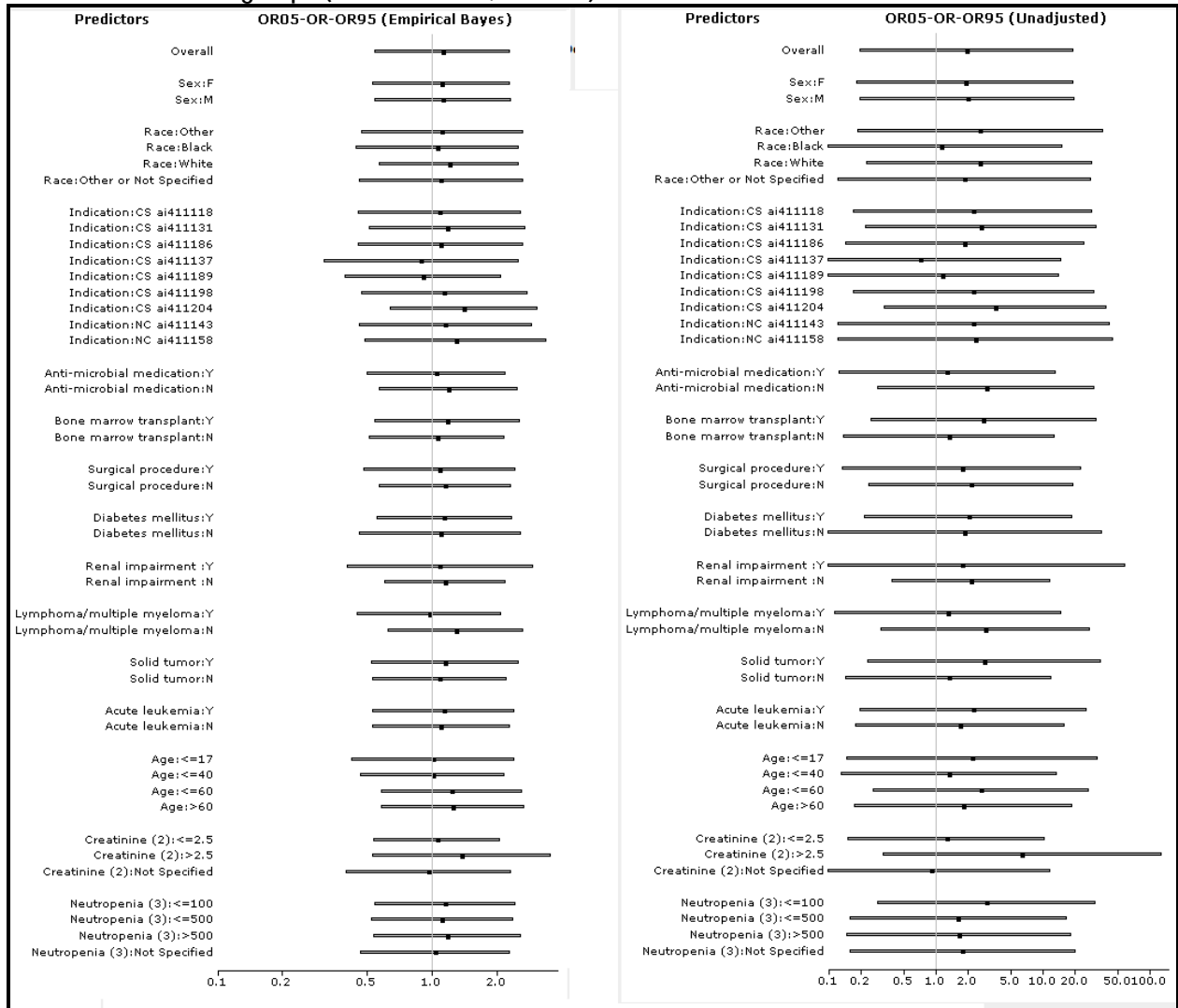
Table 5: Odds Ratios comparing covariate subgroups within the comparator arm (Issue = 'Death', run 923, same data as in Figure 5)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Sex:F	0.903	1.01	1.13	0.769	1.009	1.325	52	620
Sex:M	0.885	0.99	1.107	0.755	0.991	1.301	62	782
Race:Other	0.666	0.969	1.409	0.316	0.808	2.064	7	92
Race:Black	0.908	1.293	1.842	0.822	1.886	4.323	11	66
Race:White	0.699	0.938	1.259	0.365	0.771	1.629	79	908
Race:Other or Not Specified	0.527	0.851	1.374	0.153	0.852	4.746	17	336
Indication:CS ai411118	0.671	0.986	1.449	0.41	0.963	2.261	9	107
Indication:CS ai411131	0.754	1.081	1.55	0.581	1.32	2.996	15	179
Indication:CS ai411186	0.451	0.824	1.504	0.125	0.857	5.861	17	336

30

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Indication:CS ai411137	0.449	0.791	1.394	0.139	0.522	1.963	1	70
Indication:CS ai411189	0.684	0.95	1.32	0.555	1.143	2.353	18	263
Indication:CS ai411198	0.636	0.95	1.42	0.355	0.859	2.079	8	103
Indication:CS ai411204	0.912	1.264	1.75	0.614	1.298	2.745	34	242
Indication:NC ai411143	0.616	1.06	1.824	0.232	1.151	5.709	8	76
Indication:NC ai411158	0.653	1.189	2.164	0.232	1.199	6.184	4	26
Anti-microbial medication:Y	0.877	1.012	1.168	0.85	1.222	1.756	70	774
Anti-microbial medication:N	0.856	0.988	1.14	0.569	0.818	1.176	44	628
Bone marrow transplant:Y	0.824	0.982	1.171	0.535	0.833	1.297	19	321
Bone marrow transplant:N	0.854	1.018	1.214	0.771	1.201	1.871	95	1081
Surgical procedure:Y	0.795	0.981	1.211	0.522	0.894	1.532	7	61
Surgical procedure:N	0.826	1.019	1.258	0.653	1.118	1.916	107	1341
Diabetes mellitus:Y	0.804	1.119	1.557	0.333	1.169	4.1	97	1066
Diabetes mellitus:N	0.642	0.894	1.244	0.244	0.855	3	17	336
Renal impairment :Y	0.634	0.974	1.497	0.193	0.763	3.023	0	3
Renal impairment :N	0.668	1.026	1.577	0.331	1.31	5.186	114	1399
Lymphoma/multiple myeloma:Y	0.861	1.005	1.173	0.68	1.017	1.522	30	423
Lymphoma/multiple myeloma:N	0.852	0.995	1.161	0.657	0.983	1.471	84	979
Solid tumor:Y	0.725	0.875	1.055	0.318	0.521	0.852	23	284
Solid tumor:N	0.948	1.143	1.379	1.173	1.92	3.143	91	1118
Acute leukemia:Y	0.831	0.965	1.12	0.521	0.787	1.19	46	584
Acute leukemia:N	0.893	1.037	1.204	0.84	1.27	1.92	68	818
Age:<=17	0.59	0.832	1.173	0.166	0.439	1.161	4	108
Age:<=40	0.768	0.981	1.254	0.725	1.231	2.092	28	421
Age:<=60	0.776	0.975	1.226	0.578	0.964	1.607	43	571
Age:>60	0.996	1.256	1.584	1.143	1.919	3.223	39	302
Creatinine (2):<=2.5	0.682	0.965	1.365	0.468	1.019	2.216	108	1324
Creatinine (2):>2.5	0.739	1.148	1.784	0.326	1.068	3.497	2	6
Creatinine (2):Not Specified	0.619	0.903	1.318	0.374	0.919	2.257	4	72
Neutropenia (3):<=100	0.701	0.861	1.057	0.392	0.613	0.957	45	687
Neutropenia (3):<=500	0.86	1.065	1.319	0.784	1.221	1.903	35	363
Neutropenia (3):>500	0.925	1.181	1.506	0.891	1.512	2.565	19	145
Neutropenia (3):Not Specified	0.715	0.924	1.194	0.488	0.884	1.603	15	207

Table 6: Treatment-comparator Odds Ratios, overall and for covariate subgroups (Issue = 'Death', Run 923, same data as in Figure 6)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Overall	0.549	1.113	2.258	0.201	1.918	18.27	73	817
Sex:F	0.536	1.104	2.273	0.189	1.87	18.471	34	374
Sex:M	0.547	1.122	2.302	0.203	1.967	19.01	39	443
Race:Other	0.474	1.112	2.607	0.19	2.57	34.761	5	58
Race:Black	0.446	1.052	2.484	0.088	1.127	14.392	4	31
Race:White	0.574	1.195	2.488	0.234	2.535	27.505	51	499

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Race:Other or Not Specified	0.463	1.096	2.596	0.126	1.842	26.873	13	229
Indication:CS ai411118	0.458	1.079	2.542	0.174	2.203	27.827	5	54
Indication:CS ai411131	0.515	1.174	2.676	0.225	2.6	30.029	9	95
Indication:CS ai411186	0.456	1.092	2.616	0.147	1.851	23.357	13	229
Indication:CS ai411137	0.317	0.885	2.475	0.035	0.704	14.237	0	35
Indication:CS ai411189	0.398	0.905	2.056	0.098	1.149	13.468	8	136
Indication:CS ai411198	0.476	1.138	2.721	0.173	2.236	28.947	5	49
Indication:CS ai411204	0.643	1.401	3.05	0.34	3.561	37.265	21	117
Indication:NC ai411143	0.464	1.151	2.855	0.124	2.219	39.852	8	76
Indication:NC ai411158	0.494	1.289	3.364	0.125	2.311	42.781	4	26
Anti-microbial medication:Y	0.502	1.038	2.147	0.127	1.262	12.582	40	422
Anti-microbial medication:N	0.576	1.194	2.474	0.294	2.913	28.889	33	395
Bone marrow transplant:Y	0.547	1.176	2.527	0.252	2.772	30.453	14	195
Bone marrow transplant:N	0.518	1.053	2.144	0.141	1.326	12.458	59	622
Surgical procedure:Y	0.483	1.078	2.406	0.139	1.748	21.973	4	32
Surgical procedure:N	0.575	1.149	2.297	0.241	2.103	18.359	69	785
Diabetes mellitus:Y	0.557	1.137	2.321	0.223	2.001	17.967	60	588
Diabetes mellitus:N	0.466	1.09	2.551	0.099	1.838	34.1	13	229
Renal impairment :Y	0.406	1.084	2.895	0.054	1.737	55.75	0	2
Renal impairment :N	0.607	1.142	2.148	0.399	2.117	11.223	73	815
Lymphoma/multiple myeloma:Y	0.454	0.966	2.055	0.116	1.282	14.165	14	249
Lymphoma/multiple myeloma:N	0.628	1.283	2.619	0.312	2.869	26.411	59	568
Solid tumor:Y	0.53	1.148	2.487	0.238	2.813	33.241	18	152
Solid tumor:N	0.533	1.079	2.185	0.148	1.307	11.584	55	665
Acute leukemia:Y	0.536	1.127	2.372	0.201	2.213	24.419	32	354
Acute leukemia:N	0.536	1.099	2.251	0.181	1.662	15.25	41	463
Age:<=17	0.425	1.002	2.365	0.152	2.166	30.97	3	57
Age:<=40	0.47	1	2.128	0.136	1.332	13.045	17	266
Age:<=60	0.587	1.229	2.572	0.266	2.612	25.686	31	339
Age:>60	0.587	1.246	2.647	0.177	1.794	18.194	22	155
Creatinine (2):<=2.5	0.543	1.054	2.046	0.154	1.242	10.002	69	771
Creatinine (2):>2.5	0.533	1.363	3.488	0.333	6.341	120.863	2	2
Creatinine (2):Not Specified	0.4	0.959	2.297	0.071	0.895	11.211	2	44
Neutropenia (3):<=100	0.548	1.146	2.394	0.29	2.915	29.318	33	401
Neutropenia (3):<=500	0.525	1.108	2.339	0.161	1.605	15.955	21	214
Neutropenia (3):>500	0.538	1.171	2.55	0.153	1.645	17.705	10	81
Neutropenia (3):Not Specified	0.47	1.031	2.264	0.161	1.757	19.141	9	121

3.2.9. *Counts by Covariate with and without the Issue 'Death'*

In the following section, this reviewer pasted screen shots showing the counts by unique patients obtained by drilling down from each estimated adjusted EBOR or unadjusted OR from *any* MBLR run figure in the pool of 9 studies (for example from Figure 5 and Figure 6 (a run with 9 studies that included 7 comparative plus 2 non-comparative studies). Note in the next figures, the hyperlinked counts (in blue) that enable drilling down to the individual patient profiles behind each estimate (not shown, available upon request).

The overall enrollment across the pool of 9 studies was 58.7% for cefepime and 41.3% for the comparator (See "Combined Subgroups" in the next set of figures).

Cefepime patients had higher percentages of enrollment than their overall enrollment with several covariates, including: Sex:F, Anti-microbial medication:N, Bone marrow transplant:Y, Diabetes mellitus:N, Acute leukemia:Y (AL:Y), and Age:<=40.

Comparator patients had higher percentages of enrollment than their overall enrollment with several covariates, including: Anti-microbial medication:Y, Diabetes mellitus:Y, Solid tumor:Y, and Age:>60 (Note that Y=Yes and N=No) (next sets of figures).

Figure 7: Counts by sex

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Hide Other Levels

Sex: F

	Treatment	Comparator	Total
With Issue	34 (5% / 8% / 65%)	18 (2% / 6% / 34%)	52 (7%)
Without Issue	374 (55% / 91% / 60%)	246 (36% / 93% / 39%)	620 (92%)
Total	408 (60%)	264 (39%)	672

Chi = 0.718 (1 df)
Fisher's Exact Test = 0.555

Sex: M

	Treatment	Comparator	Total
With Issue	39 (4% / 8% / 62%)	23 (2% / 6% / 37%)	62 (7%)
Without Issue	443 (52% / 91% / 56%)	339 (40% / 93% / 43%)	782 (92%)
Total	482 (57%)	362 (42%)	844

Chi = 0.958 (1 df)
Fisher's Exact Test = 0.354

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 8: Counts by race

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Hide Other Levels

Race: Other

	Treatment	Comparator	Total
With Issue	5 (5% / 7% / 71%)	2 (2% / 5% / 28%)	7 (7%)
Without Issue	58 (58% / 92% / 63%)	34 (34% / 94% / 36%)	92 (92%)
Total	63 (63%)	36 (36%)	99

Chi = 0.445 (1 df)
Fisher's Exact Test = 1.0

Race: Black

	Treatment	Comparator	Total
With Issue	4 (5% / 11% / 36%)	7 (9% / 16% / 63%)	11 (14%)
Without Issue	31 (40% / 88% / 46%)	35 (45% / 83% / 53%)	66 (85%)
Total	35 (45%)	42 (54%)	77

Chi = -0.654 (1 df)
Fisher's Exact Test = 0.745

Race: White

	Treatment	Comparator	Total
With Issue	51 (5% / 9% / 64%)	28 (2% / 6% / 35%)	79 (8%)
Without Issue	499 (50% / 90% / 54%)	409 (41% / 93% / 45%)	908 (91%)
Total	550 (55%)	437 (44%)	987

Chi = 1.648 (1 df)
Fisher's Exact Test = 0.124

Race: Other or Not Specified

	Treatment	Comparator	Total
With Issue	13 (3% / 5% / 76%)	4 (1% / 3% / 23%)	17 (4%)
Without Issue	229 (64% / 94% / 68%)	107 (30% / 96% / 31%)	336 (95%)
Total	242 (68%)	111 (31%)	353

Chi = 0.72 (1 df)
Fisher's Exact Test = 0.598

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 9: Counts by study

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Study: CS ai411118

	Treatment	Comparator	Total
With Issue	5 (4% / 8% / 55%)	4 (3% / 7% / 44%)	9 (7%)
Without Issue	54 (46% / 91% / 50%)	53 (45% / 92% / 49%)	107 (92%)
Total	59 (50%)	57 (49%)	116

Chi = 0.293 (1 df)
Fisher's Exact Test = 1.0

Study: CS ai411198

	Treatment	Comparator	Total
With Issue	5 (4% / 9% / 62%)	3 (2% / 5% / 37%)	8 (7%)
Without Issue	49 (44% / 90% / 47%)	54 (48% / 94% / 52%)	103 (92%)
Total	54 (48%)	57 (51%)	111

Chi = 0.814 (1 df)
Fisher's Exact Test = 0.482

Study: CS ai411131

	Treatment	Comparator	Total
With Issue	9 (4% / 8% / 60%)	6 (3% / 6% / 40%)	15 (7%)
Without Issue	95 (48% / 91% / 53%)	84 (43% / 93% / 46%)	179 (92%)
Total	104 (53%)	90 (46%)	194

Chi = 0.517 (1 df)
Fisher's Exact Test = 0.789

Study: CS ai411204

	Treatment	Comparator	Total
With Issue	21 (7% / 15% / 61%)	13 (4% / 9% / 38%)	34 (12%)
Without Issue	117 (42% / 84% / 48%)	125 (45% / 90% / 51%)	242 (87%)
Total	138 (50%)	138 (50%)	276

Chi = 1.465 (1 df)
Fisher's Exact Test = 0.199

Study: CS ai411186

	Treatment	Comparator	Total
With Issue	13 (3% / 5% / 76%)	4 (1% / 3% / 23%)	17 (4%)
Without Issue	229 (64% / 94% / 68%)	107 (30% / 96% / 31%)	336 (95%)
Total	242 (68%)	111 (31%)	353

Chi = 0.72 (1 df)
Fisher's Exact Test = 0.598

Study: NC ai411143

	Treatment	Comparator	Total
With Issue	8 (9% / 9% / 100%)	0 (0% / 0% / 0%)	8 (9%)
Without Issue	76 (90% / 90% / 100%)	0 (0% / 0% / 0%)	76 (90%)
Total	84 (100%)	0 (0%)	84

Chi = 0.0 (1 df)
Fisher's Exact Test = 1.0

Study: CS ai411137

	Treatment	Comparator	Total
With Issue	0 (0% / 0% / 0%)	1 (1% / 2% / 100%)	1 (1%)
Without Issue	35 (49% / 100% / 50%)	35 (49% / 97% / 50%)	70 (98%)
Total	35 (49%)	36 (50%)	71

Chi = -0.993 (1 df)
Fisher's Exact Test = 1.0

Study: NC ai411158

	Treatment	Comparator	Total
With Issue	4 (13% / 13% / 100%)	0 (0% / 0% / 0%)	4 (13%)
Without Issue	26 (86% / 86% / 100%)	0 (0% / 0% / 0%)	26 (86%)
Total	30 (100%)	0 (0%)	30

Chi = 0.0 (1 df)
Fisher's Exact Test = 1.0

Study: CS ai411189

	Treatment	Comparator	Total
With Issue	8 (2% / 5% / 44%)	10 (3% / 7% / 55%)	18 (6%)
Without Issue	136 (48% / 94% / 51%)	127 (45% / 92% / 48%)	263 (93%)
Total	144 (51%)	137 (48%)	281

Chi = -0.597 (1 df)
Fisher's Exact Test = 0.63

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

The following are comments from William DuMouchel regarding the "Chi" values:

Notice that the values are labeled "Chi", not "Chi-squared". To get the Chi-squared value, the Chi values need to be squared, which will always lead to a positive number. DuMouchel's provides Chi so that the reader can tell the difference quickly between positive and negative association. When Chi > 0, Observed is greater than Expected in the with-Issue/Treatment cell, and when Chi < 0, Observed is less than Expected under the independence model.

The Fishers exact test P-value is based on a two-sided hypothesis, even though Chi is reminiscent of a one-tailed test statistic.

Figure 10: Counts by anti-microbial medication (AMM)

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Anti-microbial medication: Y

Hide Other Levels

	Treatment	Comparator	Total
With Issue	40 (4% / 8% / 57%)	30 (3% / 7% / 42%)	70 (8%)
Without Issue	422 (50% / 91% / 54%)	352 (41% / 92% / 45%)	774 (91%)
Total	462 (54%)	382 (45%)	844

Chi = 0.422 (1 df)
Fisher's Exact Test = 0.708

Anti-microbial medication: N

	Treatment	Comparator	Total
With Issue	33 (4% / 7% / 75%)	11 (1% / 4% / 25%)	44 (6%)
Without Issue	395 (58% / 92% / 62%)	233 (34% / 95% / 37%)	628 (93%)
Total	428 (63%)	244 (36%)	672

Chi = 1.614 (1 df)
Fisher's Exact Test = 0.144

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 11: Counts by bone marrow transplant (BMT)

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Bone marrow transplant: Y

	Treatment	Comparator	Total
With Issue	14 (4% / 6% / 73%)	5 (1% / 3% / 26%)	19 (5%)
Without Issue	195 (57% / 93% / 60%)	126 (37% / 96% / 39%)	321 (94%)
Total	209 (61%)	131 (38%)	340

Chi = 1.126 (1 df)
Fisher's Exact Test = 0.335

Bone marrow transplant: N

	Treatment	Comparator	Total
With Issue	59 (5% / 8% / 62%)	36 (3% / 7% / 37%)	95 (8%)
Without Issue	622 (52% / 91% / 57%)	459 (39% / 92% / 42%)	1081 (91%)
Total	681 (57%)	495 (42%)	1176

Chi = 0.864 (1 df)
Fisher's Exact Test = 0.448

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 12: Counts by surgical procedure

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Surgical procedure: Y

	Treatment	Comparator	Total
With Issue	4 (5% / 11% / 57%)	3 (4% / 9% / 42%)	7 (10%)
Without Issue	32 (47% / 88% / 52%)	29 (42% / 90% / 47%)	61 (89%)
Total	36 (52%)	32 (47%)	68

Chi = 0.235 (1 df)
Fisher's Exact Test = 1.0

Surgical procedure: N

	Treatment	Comparator	Total
With Issue	69 (4% / 8% / 64%)	38 (2% / 6% / 35%)	107 (7%)
Without Issue	785 (54% / 91% / 58%)	556 (38% / 93% / 41%)	1341 (92%)
Total	854 (58%)	594 (41%)	1448

Chi = 1.204 (1 df)
Fisher's Exact Test = 0.261

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 13: Counts by diabetes mellitus

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Diabetes mellitus: Y

[Hide Other Levels]

	Treatment	Comparator	Total
With Issue	60 (5% / 9% / 61%)	37 (3% / 7% / 38%)	97 (8%)
Without Issue	588 (50% / 90% / 55%)	478 (41% / 92% / 44%)	1066 (91%)
Total	648 (55%)	515 (44%)	1163

Chi = 1.271 (1 df)
Fisher's Exact Test = 0.24

Diabetes mellitus: N

	Treatment	Comparator	Total
With Issue	13 (3% / 5% / 76%)	4 (1% / 3% / 23%)	17 (4%)
Without Issue	229 (64% / 94% / 68%)	107 (30% / 96% / 31%)	336 (95%)
Total	242 (68%)	111 (31%)	353

Chi = 0.72 (1 df)
Fisher's Exact Test = 0.598

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 14: Counts by renal impairment

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Hide Other Levels

Renal impairment : Y

	Treatment	Comparator	Total
With Issue	0 (0% / 0% / 0%)	0 (0% / 0% / 0%)	0 (0%)
Without Issue	2 (66% / 100% / 66%)	1 (33% / 100% / 33%)	3 (100%)
Total	2 (66%)	1 (33%)	3

Chi = 0.0 (1 df)
Fisher's Exact Test = 1.0

Renal impairment : N

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	815 (53% / 91% / 58%)	584 (38% / 93% / 41%)	1399 (92%)
Total	888 (58%)	625 (41%)	1513

Chi = 1.205 (1 df)
Fisher's Exact Test = 0.237

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 15: Counts by lymphoma/multiple myeloma

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Lymphoma/multiple myeloma: Y

	Treatment	Comparator	Total
With Issue	14 (3% / 5% / 46%)	16 (3% / 8% / 53%)	30 (6%)
Without Issue	249 (54% / 94% / 58%)	174 (38% / 91% / 41%)	423 (93%)
Total	263 (58%)	190 (41%)	453

Chi = -1.308 (1 df)
Fisher's Exact Test = 0.25

Lymphoma/multiple myeloma: N

	Treatment	Comparator	Total
With Issue	59 (5% / 9% / 70%)	25 (2% / 5% / 29%)	84 (7%)
Without Issue	568 (53% / 90% / 58%)	411 (38% / 94% / 41%)	979 (92%)
Total	627 (58%)	436 (41%)	1063

Chi = 2.185 (1 df)
Fisher's Exact Test = 0.037

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 16: Counts by solid tumor (ST)

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Solid tumor: Y

	Treatment	Comparator	Total
With Issue	18 (5% / 10% / 78%)	5 (1% / 3% / 21%)	23 (7%)
Without Issue	152 (49% / 89% / 53%)	132 (42% / 96% / 46%)	284 (92%)
Total	170 (55%)	137 (44%)	307

Chi = 2.296 (1 df)
Fisher's Exact Test = 0.028

Solid tumor: N

	Treatment	Comparator	Total
With Issue	55 (4% / 7% / 60%)	36 (2% / 7% / 39%)	91 (7%)
Without Issue	665 (55% / 92% / 59%)	453 (37% / 92% / 40%)	1118 (92%)
Total	720 (59%)	489 (40%)	1209

Chi = 0.179 (1 df)
Fisher's Exact Test = 0.912

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 17: Counts by acute leukemia (AL)

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Acute leukemia: Y

	Treatment	Comparator	Total
With Issue	32 (5% / 8% / 69%)	14 (2% / 5% / 30%)	46 (7%)
Without Issue	354 (56% / 91% / 60%)	230 (36% / 94% / 39%)	584 (92%)
Total	386 (61%)	244 (38%)	630

Chi = 1.2 (1 df)
Fisher's Exact Test = 0.272

Acute leukemia: N

	Treatment	Comparator	Total
With Issue	41 (4% / 8% / 60%)	27 (3% / 7% / 39%)	68 (7%)
Without Issue	463 (52% / 91% / 56%)	355 (40% / 92% / 43%)	818 (92%)
Total	504 (56%)	382 (43%)	886

Chi = 0.591 (1 df)
Fisher's Exact Test = 0.611

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 18: Counts by age

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

[Hide Other Levels]

Age: <=17

	Treatment	Comparator	Total
With Issue	3 (2% / 5% / 75%)	1 (0% / 1% / 25%)	4 (3%)
Without Issue	57 (50% / 95% / 52%)	51 (45% / 98% / 47%)	108 (96%)
Total	60 (53%)	52 (46%)	112

Chi = 0.875 (1 df)
Fisher's Exact Test = 0.622

Age: <=40

	Treatment	Comparator	Total
With Issue	17 (3% / 6% / 60%)	11 (2% / 6% / 39%)	28 (6%)
Without Issue	266 (59% / 93% / 63%)	155 (34% / 93% / 36%)	421 (93%)
Total	283 (63%)	166 (36%)	449

Chi = -0.262 (1 df)
Fisher's Exact Test = 0.841

Age: <=60

	Treatment	Comparator	Total
With Issue	31 (5% / 8% / 72%)	12 (1% / 4% / 27%)	43 (7%)
Without Issue	339 (55% / 91% / 59%)	232 (37% / 95% / 40%)	571 (92%)
Total	370 (60%)	244 (39%)	614

Chi = 1.644 (1 df)
Fisher's Exact Test = 0.108

Age: >60

	Treatment	Comparator	Total
With Issue	22 (6% / 12% / 56%)	17 (4% / 10% / 43%)	39 (11%)
Without Issue	155 (45% / 87% / 51%)	147 (43% / 89% / 48%)	302 (88%)
Total	177 (51%)	164 (48%)	341

Chi = 0.598 (1 df)
Fisher's Exact Test = 0.611

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Figure 19: Counts by serum creatinine

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not at all

Creatinine (2): <=2.5

	Treatment	Comparator	Total
With Issue	69 (4% / 8% / 63%)	39 (2% / 6% / 36%)	108 (7%)
Without Issue	771 (53% / 91% / 58%)	553 (38% / 93% / 41%)	1324 (92%)
Total	840 (58%)	592 (41%)	1432

Chi = 1.148 (1 df)
Fisher's Exact Test = 0.265

Creatinine (2): >2.5

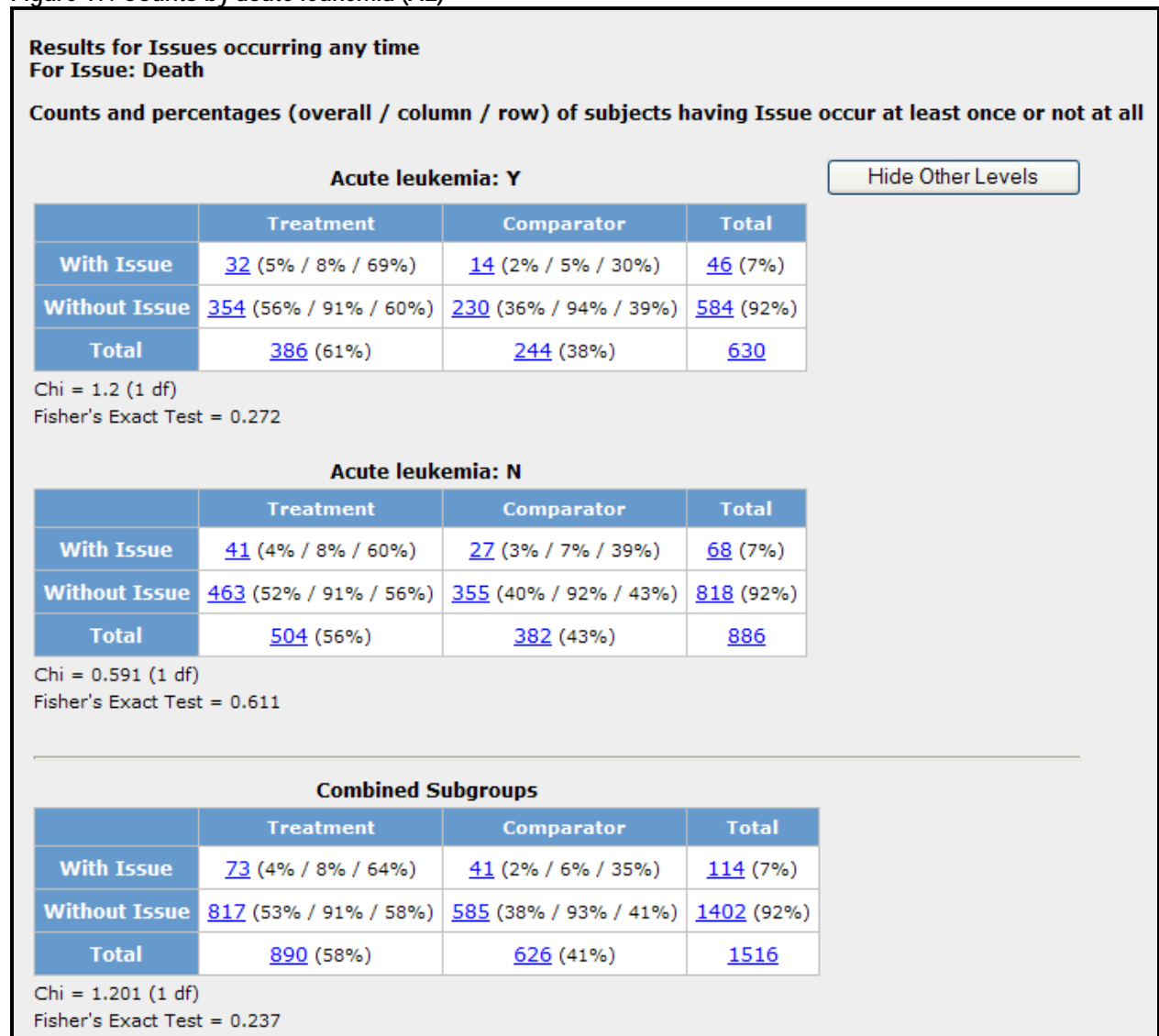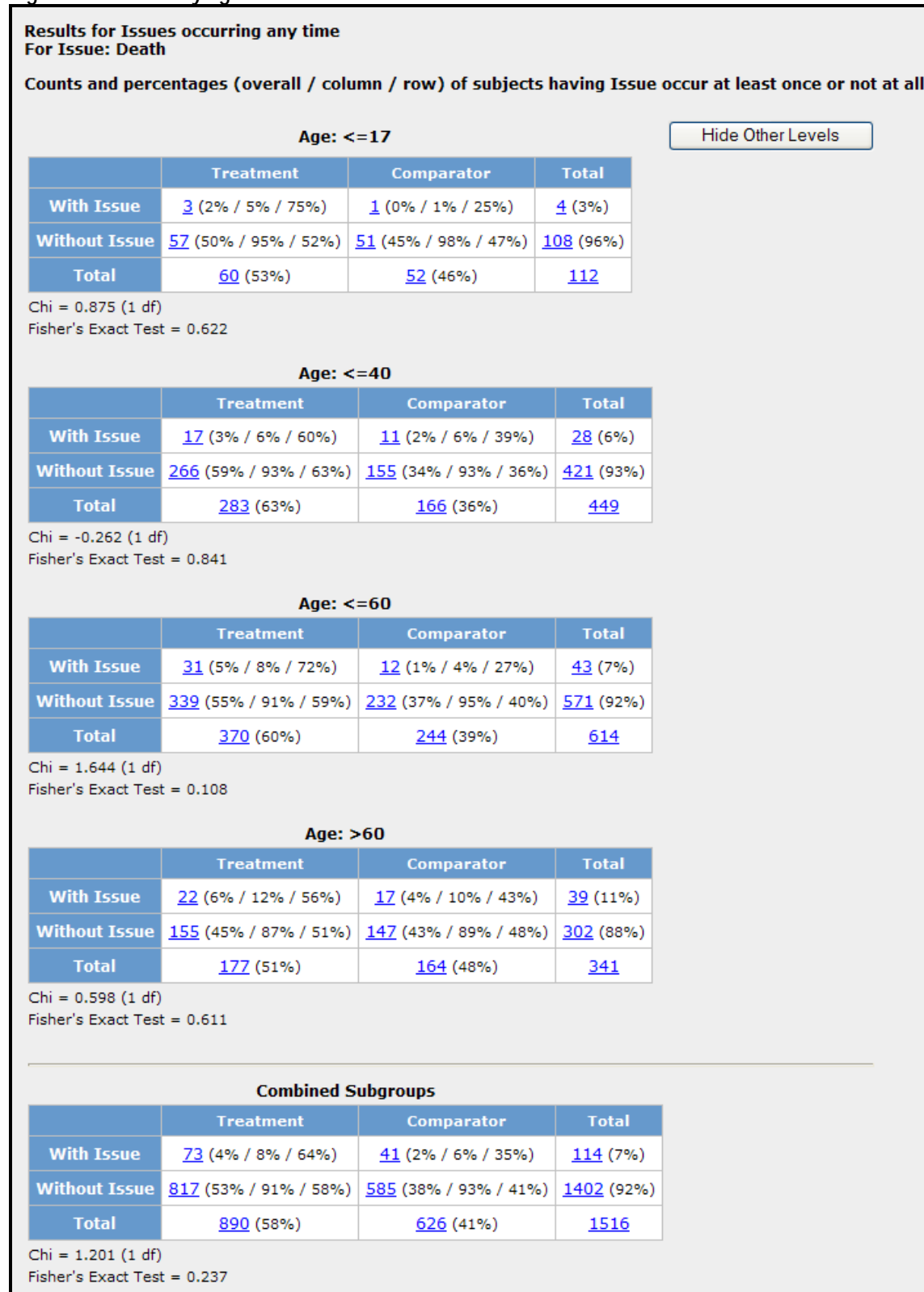|	Treatment	Comparator	Total
With Issue	2 (25% / 50% / 100%)	0 (0% / 0% / 0%)	2 (25%)
Without Issue	2 (25% / 50% / 33%)	4 (50% / 100% / 66%)	6 (75%)
Total	4 (50%)	4 (50%)	8

Chi = 1.633 (1 df)
Fisher's Exact Test = 0.429

Creatinine (2): Not Specified

	Treatment	Comparator	Total
With Issue	2 (2% / 4% / 50%)	2 (2% / 6% / 50%)	4 (5%)
Without Issue	44 (57% / 95% / 61%)	28 (36% / 93% / 38%)	72 (94%)
Total	46 (60%)	30 (39%)	76

Chi = -0.443 (1 df)
Fisher's Exact Test = 0.645

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

Figure 20: Counts by neutrophil count

Results for Issues occurring any time
For Issue: Death

Counts and percentages (overall / column / row) of subjects having Issue occur at least once or not a

Neutropenia (3): <=100

	Treatment	Comparator	Total
With Issue	33 (4% / 7% / 73%)	12 (1% / 4% / 26%)	45 (6%)
Without Issue	401 (54% / 92% / 58%)	286 (39% / 95% / 41%)	687 (93%)
Total	434 (59%)	298 (40%)	732

Chi = 1.979 (1 df)
Fisher's Exact Test = 0.059

Neutropenia (3): <=500

	Treatment	Comparator	Total
With Issue	21 (5% / 8% / 60%)	14 (3% / 8% / 40%)	35 (8%)
Without Issue	214 (53% / 91% / 58%)	149 (37% / 91% / 41%)	363 (91%)
Total	235 (59%)	163 (40%)	398

Chi = 0.12 (1 df)
Fisher's Exact Test = 1.0

Neutropenia (3): >500

	Treatment	Comparator	Total
With Issue	10 (6% / 10% / 52%)	9 (5% / 12% / 47%)	19 (11%)
Without Issue	81 (49% / 89% / 55%)	64 (39% / 87% / 44%)	145 (88%)
Total	91 (55%)	73 (44%)	164

Chi = -0.266 (1 df)
Fisher's Exact Test = 0.811

Neutropenia (3): Not Specified

	Treatment	Comparator	Total
With Issue	9 (4% / 6% / 60%)	6 (2% / 6% / 40%)	15 (6%)
Without Issue	121 (54% / 93% / 58%)	86 (38% / 93% / 41%)	207 (93%)
Total	130 (58%)	92 (41%)	222

Chi = 0.117 (1 df)
Fisher's Exact Test = 1.0

Combined Subgroups

	Treatment	Comparator	Total
With Issue	73 (4% / 8% / 64%)	41 (2% / 6% / 35%)	114 (7%)
Without Issue	817 (53% / 91% / 58%)	585 (38% / 93% / 41%)	1402 (92%)
Total	890 (58%)	626 (41%)	1516

Chi = 1.201 (1 df)
Fisher's Exact Test = 0.237

Hide Other Levels

3.2.10. *Simplification of the MBLR Model*

We simplified the MBLR model by selecting only the predictors (not the responses) that could make a difference (See Table 8). We removed the predictors with CI that overlapped the most within the "comparator arm only" analysis (for example, we removed Sex to produce the simplified model because the CI for "Sex: F" and "Sex: M" overlapped the most, see Figure 5). The predictors selected in the simplified model contained the covariates showing the most non-overlapping results within the comparator arm only.

To simplify the predictors (not to select responses), we first included in the MBLR model to analyze 'Death' as many predictors (covariates) as we felt were necessary (Table 3). Once we looked at all the predictors, we simplified the model by selecting for further analysis the predictors that could make a difference (the ones showing the most non-overlapping results within the comparator arm).

3.2.11. *Validation of the Consistency the Results of 25 MBLR Runs*

3.2.11.1. *Choices of Covariates and Issues*

We studied the effect of borrowing strength by reducing the number of issues in the MBLR model, the effect of *not* borrowing strength, and of borrowing strength from a comparator cluster of issues (Table 7 and Table 8).

We also produced MBLR analyses that only included study arm, study, age and race, and sequentially removed from the analysis AL, BMT, NEU, and ST as detailed in Table 8.

Table 7: Number of issues and type of issues selected to borrow strength

Issues	Issues long names
1 Issue: Death only	PT: Death
2 Issues: Death + 1 CEF* Issue (CHC)	PT: Death, SMQ: CNS haemorrhages and cerebrovascular accidents [narrow]
2 Issues: Death + 1 CEF Issue (HCC**)	PT: Death, SMQ: Haemorrhagic cerebrovascular conditions [narrow]
2 Issues: Death + 1 CEF Issue (VHD)	PT: Death, HLT: Vascular hypotensive disorders
6 Issues: Death + 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)	PT: Death, PT: Abdominal distension, PT: Hypertension, PT: Jaundice, PT: Rales, SMQ: Biliary disorders (SMQ) [narrow]
6 Issues: Death + 5 COMP*** Issues (AD, HT, J, R, BD)	PT: Death, SMQ: Haemorrhagic cerebrovascular conditions [narrow]**, HLT: Central nervous system haemorrhages and cerebrovascular accidents, HLT: Vascular hypotensive disorders, SMQ: Cerebrovascular disorders [narrow], SMQ: CNS haemorrhages and cerebrovascular accidents [narrow]

* CEF: Cefepime-related issues
** HCC: Issue with highest SOR score associated with 'Death' in a syndromic cluster
** COMP: Comparator-related issues

The following table describes the covariates and issues selected in each of the 25 different MBLR runs

Table 8: Number and types of covariates and issues used in 25 different MBLR runs by run number

Run	Covariates	Issues
921	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF* Issue (CHC)
920	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)
922	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6	2 Issues: Death, 1 CEF Issue (VHD)

Run	Covariates	Issues
	Other	
919	14 Covariates: 7 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)
923	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
924	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 COMP** Issues (AD, HT, J, R, BD)
927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	2 Issues: Death, 1 CEF Issue (HCC)
928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1 Issue: Death only
870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)
628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)
881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only
670	5 Covariates: 9 Studies + Age + Race + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)
926	5 Covariates: 9 Studies + Age + Race + BMT + NEU	2 Issues: Death, 1 CEF Issue (HCC)
629	5 Covariates: 9 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)
925	5 Covariates: 9 Studies + Age + Race + AL + NEU	2 Issues: Death, 1 CEF Issue (HCC)
668	5 Covariates: 9 Studies + Age + Race + AL + BMT	2 Issues: Death, 1 CEF Issue (HCC)
874	5 Covariates: 7 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)
631	4 Covariates: 9 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)
929	4 Covariates: 9 Studies + Age + Race + NEU	2 Issues: Death, 1 CEF Issue (HCC)
671	4 Covariates: 9 Studies + Age + Race + BMT	2 Issues: Death, 1 CEF Issue (HCC)
632	4 Covariates: 9 Studies + Age + Race + AL	2 Issues: Death, 1 CEF Issue (HCC)
871	4 Covariates: 7 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)
873	4 Covariates: 7 Studies + Age + Race + AL	2 Issues: Death, 1 CEF Issue (HCC)
672	3 Covariates: 9 Studies + Age + Race	2 Issues: Death, 1 CEF Issue (HCC)
675	3 Covariates: 9 Studies + Age + Race	1 Issue: Death only

* Same 14 covariates as listed in Table 3
** CEF: Cefepime-related issues
*** COMP: Comparator-related issues

3.3. Results

3.3.1. Death Estimates in 25 MBLR Runs

3.3.1.1. Adjusted Estimates

The adjusted estimates for the 'Death' issue across 25 MBLR runs did not indicate the presence of a statistically significant large death effect.

In every one of the 25 MBLR runs the Bayesian effect for 'Death' shrunk toward 1, and it happened regardless of the issues we put in the model.

The overall EBOR values were 1.162 [1.162 (0.731, 1.848)] or lower and the CIs included 1, reaching in some cases EBOR values that were very close to 1.

We obtained the widest confidence when we selected to analyze 14 covariates. We obtained the narrowest confidence limits when we reduced the number of covariates from 14 to 7 or less.

Regardless of the number of predictors that we used in the 25 MBLR runs, we never observed a EBOR05 >1 for the overall (Table 9, Table 10), or for any of the predictors or covariates that we used. The adjusted CIs of each of the covariate-defined subgroups overlapped the adjusted overall CI and included 1.

When we simplified the model by removing covariates, the confidence limits became narrower, and the EBOR values for the overall became closer to 1 (See Table 9, Table 10, and Figure 21 (repeated as Figure 48))

The selection of cefepime or comparator issues to borrow strength, or the selection of different number of issues besides 'Death' to borrow strength, did not change the overall EBOR values for 'Death.'.

Table 9: Overall EBOR and OR values for death by the covariates and issue(s) selected in 25 MBLR runs (rows ranked by ascending EBOR values)

Run	Covariates	Issues****	EBOR	OR****
675	3 Covariates: 9 Studies + Age + Race	1 Issue: Death only	-1	1.045
881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only	-1	2.129
928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1 Issue: Death only	-1	2.067
873	4 Covariates: 7 Studies + Age + Race + AL	2 Issues: Death, 1 CEF* Issue (HCC)**	1.05	0.962
871	4 Covariates: 7 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.054	1.303
874	5 Covariates: 7 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.065	1.506
929	4 Covariates: 9 Studies + Age + Race + NEU	2 Issues: Death, 1 CEF Issue (HCC)	1.079	0.991
925	5 Covariates: 9 Studies + Age + Race + AL + NEU	2 Issues: Death, 1 CEF Issue (HCC)	1.082	1.007
672	3 Covariates: 9 Studies + Age + Race	2 Issues: Death, 1 CEF Issue (HCC)	1.093	1.045
632	4 Covariates: 9 Studies + Age + Race + AL	2 Issues: Death, 1 CEF Issue (HCC)	1.095	1.058
870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.102	1.932
924	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 COMP*** Issues (AD, HT, J, R, BD)	1.11	1.918
926	5 Covariates: 9 Studies + Age + Race + BMT + NEU	2 Issues: Death, 1 CEF Issue (HCC)	1.11	1.133
631	4 Covariates: 9 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.113	1.498
922	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (VHD)	1.113	1.918
923	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)	1.113	1.918
921	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (CHC)	1.119	1.918
919	14 Covariates: 7 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)	1.12	2.204
920	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)	1.12	1.918
629	5 Covariates: 9 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.121	1.696
671	4 Covariates: 9 Studies + Age + Race + BMT	2 Issues: Death, 1 CEF Issue (HCC)	1.124	1.187
668	5 Covariates: 9 Studies + Age + Race + AL + BMT	2 Issues: Death, 1 CEF Issue (HCC)	1.132	1.247
670	5 Covariates: 9 Studies + Age + Race + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.146	1.72
927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.149	2.067
628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	1.162	2.129

* CEF: Cefepime-related issues
** HCC: Issue with highest SOR associated with 'Death' in a syndromic cluster
*** COMP: Comparator-related issues
**** Issues to borrow strength are used to calculate EBOR, not OR

Table 10: Overall EBOR values for death by type of MBLR run ranked by ascending EBOR values

Run	Covariates	Issues	EBOR05	EBOR	EBOR95

Run	Covariates	Issues	EBOR05	EBOR	EBOR95
675	3 Covariates: 9 Studies + Age + Race	1 Issue: Death only	-1	-1	-1
881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only	-1	-1	-1
928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1 Issue: Death only	-1	-1	-1
873	4 Covariates: 7 Studies + Age + Race + AL	2 Issues: Death, 1 CEF* Issue (HCC)	0.708	1.05	1.559
871	4 Covariates: 7 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)**	0.69	1.054	1.612
874	5 Covariates: 7 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.692	1.065	1.639
929	4 Covariates: 9 Studies + Age + Race + NEU	2 Issues: Death, 1 CEF Issue (HCC)	0.715	1.079	1.628
925	5 Covariates: 9 Studies + Age + Race + AL + NEU	2 Issues: Death, 1 CEF Issue (HCC)	0.716	1.082	1.635
672	3 Covariates: 9 Studies + Age + Race	2 Issues: Death, 1 CEF Issue (HCC)	0.733	1.093	1.63
632	4 Covariates: 9 Studies + Age + Race + AL	2 Issues: Death, 1 CEF Issue (HCC)	0.732	1.095	1.639
870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.693	1.102	1.752
924	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 COMP*** Issues (AD, HT, J, R, BD)	0.561	1.11	2.196
926	5 Covariates: 9 Studies + Age + Race + BMT + NEU	2 Issues: Death, 1 CEF Issue (HCC)	0.715	1.11	1.722
631	4 Covariates: 9 Studies + Age + Race + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.726	1.113	1.707
922	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (VHD)	0.439	1.113	2.819
923	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)	0.549	1.113	2.258
921	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (CHC)	0.418	1.119	2.991
919	14 Covariates: 7 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)	0.413	1.12	3.039
920	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	2 Issues: Death, 1 CEF Issue (HCC)	0.417	1.12	3.004
629	5 Covariates: 9 Studies + Age + Race + AL + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.726	1.121	1.73
671	4 Covariates: 9 Studies + Age + Race + BMT	2 Issues: Death, 1 CEF Issue (HCC)	0.733	1.124	1.724
668	5 Covariates: 9 Studies + Age + Race + AL + BMT	2 Issues: Death, 1 CEF Issue (HCC)	0.736	1.132	1.742
670	5 Covariates: 9 Studies + Age + Race + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.726	1.146	1.807
927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.714	1.149	1.849
628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	2 Issues: Death, 1 CEF Issue (HCC)	0.731	1.162	1.848

* CEF: Cefepime-related issues
** HCC: Issue with highest SOR associated with 'Death' in a syndromic cluster
*** COMP: Comparator-related issues

Figure 21: Overall adjusted (EBOR) values by type of covariate and issue analyzed

Issues Selected:
- 1 Issue: Death only
- 2 Issues: Death, 1 CEF Issue (CHC)
- 2 Issues: Death, 1 CEF Issue (HCC)
- 2 Issues: Death, 1 CEF Issue (VHD)
- 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

3.3.1.2.   *Unadjusted Estimates*

The unadjusted estimates were larger than the adjusted (EBOR) ones, and with much wider confidence intervals, as seen when comparing the estimates in Table 10 vs. Table 11, Figure 21 vs. Figure 22 and Figures starting on page 97 vs. the ones starting on page 140.

The unadjusted estimates for the 'Death' issue across 25 MBLR runs did not indicate the presence of a statistically significant large death effect.

Every CI for the overall OR estimate included 1 (Table 11)

Table 11: Overall unadjusted OR values for death by type of MBLR run ranked by OR values

Run	Covariates	No Issues to borrow strength*	OR05	OR	OR95
873	4 Covariates: 7 Studies + Age + Race + AL	1 Issue: Death only	0.482	0.962	1.919
929	4 Covariates: 9 Studies + Age + Race + NEU	1 Issue: Death only	0.464	0.991	2.119
925	5 Covariates: 9 Studies + Age + Race + AL + NEU	1 Issue: Death only	0.47	1.007	2.157
675	3 Covariates: 9 Studies + Age + Race	1 Issue: Death only	0.501	1.045	2.177
672	3 Covariates: 9 Studies + Age + Race	1 Issue: Death only	0.501	1.045	2.177
632	4 Covariates: 9 Studies + Age + Race + AL	1 Issue: Death only	0.506	1.058	2.212
926	5 Covariates: 9 Studies + Age + Race + BMT + NEU	1 Issue: Death only	0.494	1.133	2.599
671	4 Covariates: 9 Studies + Age + Race + BMT	1 Issue: Death only	0.532	1.187	2.648
668	5 Covariates: 9 Studies + Age + Race + AL + BMT	1 Issue: Death only	0.554	1.247	2.804
871	4 Covariates: 7 Studies + Age + Race + ST	1 Issue: Death only	0.598	1.303	2.837
631	4 Covariates: 9 Studies + Age + Race + ST	1 Issue: Death only	0.663	1.498	3.384
874	5 Covariates: 7 Studies + Age + Race + AL + ST	1 Issue: Death only	0.68	1.506	3.335
629	5 Covariates: 9 Studies + Age + Race + AL + ST	1 Issue: Death only	0.739	1.696	3.894
670	5 Covariates: 9 Studies + Age + Race + BMT + ST	1 Issue: Death only	0.714	1.72	4.142
924	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.201	1.918	18.27
922	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.201	1.918	18.27
923	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.201	1.918	18.27
921	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.201	1.918	18.27
920	14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.201	1.918	18.27
870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only	0.799	1.932	4.675
928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1 Issue: Death only	0.809	2.067	5.279
927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1 Issue: Death only	0.809	2.067	5.279
881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only	0.858	2.129	5.285
628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1 Issue: Death only	0.858	2.129	5.285
919	14 Covariates: 7 Studies + Age + Race + Sex + AL + BMT + NEU + ST + 6 Other	1 Issue: Death only	0.229	2.204	21.217

* Issues to borrow strength are used to estimate adjusted EBOR, not to estimate unadjusted OR

Figure 22: Overall unadjusted (OR) values by type of covariate analyzed

Each of the covariate-defined subgroups had CI's for OR values that overlapped the CI's for the overall OR values, and in general the CIs included 1.

The individual covariates that show OR05>1 when the following additional covariates were also included in the model, *but not when fewer or more covariates were in the model,* included (See details in Table 12):

'White race' with the following covariates in the model including: 5 covariates: 7 or 9 studies + Age + Race + AL + ST; or 5 covariates: 9 studies + Age + Race + BMT + ST; or 6 covariates: 7 or 9 studies + AL, BMT, ST; or 7 covariates: 9 studies + Age + Race + AL + NEU + ST; but not with fewer or more covariates in the model

'Study ai411204' with the following covariates in the model including: 6 covariates: 9 or 7 Studies, Age, Race, AL, BMT, and ST; or 7 covariates: 9 studies + Age + Race + AL + BMT + NEU + ST; but not with fewer or more covariates in the model

'Solid tumor (Y)' with the following covariates in the model including: 5 covariates: 9 studies + Age + Race + AL + ST; or 6 covariates: 7 or 9 studies + AL, BMT, ST; or 7 covariates: 9 studies + Age + Race + AL + NEU + ST; but not with fewer or more covariates in the model

'Acute leukemia (Y)' with the following covariates in the model including: 6 covariates: 9 or 7 Studies + Age + Race, AL, BMT + ST; but not with fewer or more covariates in the model

'Age =<60' with the following covariates in the model including: 6 covariates: 9 Studies, Age, Race, AL, BMT, and ST; or 7 covariates: 9 studies + Age + Race + AL + NEU + ST; but not with fewer or more covariates in the model

Neutropenia (3) <=100 with the following covariates in the model including: 7 covariates: 9 studies + Age + Race + AL + NEU + ST, but not with fewer or more covariates in the model

Table 12: Individual covariates with an OR05>1 for death by all the covariates included in the run (sorted by OR value)

Covariate	Rum	Covariates in the MBLR run	OR05	OR	OR95
Race:White	874	5 Covariates: 7 Studies + Age + Race + AL + ST*	1.026	2.226	4.83
Race:White	629	5 Covariates: 9 Studies + Age + Race + AL + ST	1.042	2.316	5.146
Race:White	670	5 Covariates: 9 Studies + Age + Race + BMT + ST	1.009	2.355	5.497
Race:White	927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.059	2.619	6.477
Race:White	928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.059	2.619	6.477
Age:<=60	927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.039	2.829	7.707
Age:<=60	928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.039	2.829	7.707
Race:White	870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	1.209	2.879	6.854
Age:<=60	628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.091	2.901	7.712
Age:<=60	881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.091	2.901	7.712
Race:White	628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.209	2.917	7.037
Race:White	881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.209	2.917	7.037
Neutropenia (3):<=100	927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.072	2.964	8.191
Neutropenia (3):<=100	928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.072	2.964	8.191
Acute leukemia:Y	870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	1.035	2.999	8.692
Acute leukemia:Y	628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.034	3.026	8.859
Acute leukemia:Y	881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.034	3.026	8.859
Indication:CS ai411204	927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.029	3.163	9.727
Indication:CS ai411204	928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.029	3.163	9.727
Solid tumor:Y	629	5 Covariates: 9 Studies + Age + Race + AL + ST	1.039	3.249	10.162
Indication:CS ai411204	628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.085	3.278	9.904
Indication:CS ai411204	881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.085	3.278	9.904

Covariate	Rum	Covariates in the MBLR run	OR05	OR	OR95
Indication:CS ai411204	870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	1.106	3.39	10.391
Solid tumor:Y	870	6 Covariates: 7 Studies + Age + Race + AL + BMT + ST	1.101	3.707	12.485
Solid tumor:Y	927	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.174	4.051	13.983
Solid tumor:Y	928	7 Covariates: 9 Studies + Age + Race + AL + BMT + NEU + ST	1.174	4.051	13.983
Solid tumor:Y	628	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.25	4.2	14.115
Solid tumor:Y	881	6 Covariates: 9 Studies + Age + Race + AL + BMT + ST	1.25	4.2	14.115

* The issues did not affect the unadjusted OR values. The issues to borrow strength only affected the adjusted EBOR values. The MBLR runs generate adjusted (EBOR) and unadjusted estimates (OR). Therefore, some of the OR results for different runs show duplicate OR values, since the different issues selected to study the effect on the adjusted (EBOR), did not affect the covariate selected. We present the OR values for each run for completeness.

3.4. *Conclusions*

The cefepime FN studies originally designed to answer efficacy questions do not have enough power to enable randomization to be effective in balancing confounders that could affect mortality among treatment groups.

The small size of the studies made them vulnerable to the problem of small counts and multiple comparisons issues.

The multiple episodes of FN and repeat re-randomization of these patients made these studies vulnerable to an unbalanced number of covariates by treatment.

The cefepime patients seem to have been sicker *at baseline*. There were 6.25% additional cefepime patients with AL *or* with BMT at baseline. These covariates are associated with an acute risk of death.

These studies also had 9.1% additional cefepime patients who **_did not receive_** concomitant antimicrobial medication (AMM) (Sections 3.2.2 and 3.2.3).

Our analyses of mortality risk, using primary data and the MBLR method that corrects for multiplicity and small counts, do not support the reported statistically significant mortality imbalance for FN in two meta-analyses of secondary data (1,2) that triggered the consult requested by DAIOP.

The adjusted MBLR analyses have not shown EBOR values for death and any death predictor that are significantly greater for cefepime than for the comparators.

Although the MBLR values seem to suggest a small effect in the death rate (the EBOR for the overall and covariates effects are above 1), there is no statistical evidence of an increased risk of death across 25 different MBLR runs in FN patients treated with cefepime vs. comparators.

The CIs for the overall treatment/comparator adjusted EBOR for death across multiple MBLR runs include 1. The adjusted EBOR values for specific death predictors across 25 MBLR runs show no evidence of a statistically significant increased risk for cefepime in any subgroup analyzed.

The overall EBOR values were 1.162 (0.731, 1.848) or lower and the CIs included 1, reaching in some cases EBOR values that were very close to 1.

The choice of statistical method seems to have driven the results reported by Yahav, Paul et al and by Paul, Yahav et al. These two reported meta-analyses used a fixed effects model that did not adjust for multiplicity and small counts by borrowing strength from other issues. These authors seem to have analyzed the treatment of the first episode of FN.(4)

The independent meta-analysis by Yu-te Wu dated January 14, 2009, has the characteristics of a fixed effect model weighted by the proportion of patients in each study. Like our analysis, Yu-te Wu analyzed the treatment of the most recent episode of FN. Wu also analyzed other indications beside FN that were not available in CDISC standards. Unlike our analyses, Wu did not adjust for multiplicity and small counts by borrowing strength from other issues.

In her review, Yu-te Wu found that the overall mortality risk difference in the cefepime group was greater than the comparator, but that the difference was not statistically significant.

Our unadjusted analysis shows a similar non-statistically significant effect. However, the effect becomes closer to 1 when we adjusted by borrowing strength.

The unadjusted results could be false positive results.

The unadjusted confidence limits for the overall OR values are larger, more unstable, less precise, and wider than the adjusted ones.

Every CI for the overall OR estimate included 1. Each of the covariate-defined subgroups had CI's for OR values that overlapped the CIs for overall OR values and in general included 1.

Yu-te Wu's subgroup analysis of ST at baseline not adjusted for multiplicity showed a significantly greater mortality, but with wide confidence intervals that overlapped the overall estimate. Wu concluded that there is a need to re-examine her results when more data are available because of the small numbers in this estimate.

The unadjusted estimates for the following covariates show an OR05>1 when certain covariates were included in the model, *but not when fewer or more covariates were in the model* (further up in Section 3.3.1.2 of the Medical Officer's Consult Review there is a detailed description):

> 'White race', Study ai411204', 'Solid tumor (Y)', 'Acute leukemia (Y)', 'Age =<60', Neutropenia (3) <=100.

When ST is in the model, unadjusted OR>1 estimates occur when Studies + Age + Race + AL are also included in the model with or without the addition of BMT or BMT + NEU , *but not when fewer or more covariates were in the model.*

These are definitively borderline results.

The unadjusted estimates are subject to the multiple comparison issues. One such example is the above described finding of an OR05>1 for the age category <=60 years, not detected in the age category >60 years in any of the 25 MBLR runs. This finding does not make biological sense.

3.5. *Summary*

We conclude that we cannot confirm the reported findings in two meta-analysis authored by Yahav, Paul's et al and Paul, Yahav et al of a statistically significant increase in mortality risk for cefepime vs. comparators. The overall EBOR values for death for cefepime vs. comparator were 1.162 [1.162 (0.731, 1.848)] or lower and the CIs included 1, reaching in some cases EBOR values that were very close to 1.

The adjusted MBLR analyses across 14 different predictors do not show overall EBOR values for death and for any death predictor that are significantly greater for cefepime than the comparators.

The simplification of the covariate model generates tighter confidence intervals, but no predictor that shows EBOR05>1 in any of the 25 MBLR runs.

The EBOR values across 25 MBLR runs are stable regardless of the number of cefepime or comparator issues selected to borrow strength, and regardless of selecting the population of the 7 comparative FN studies or the 9 FN comparative and non-comparative studies (7 comparative, and 2 non-comparative).

In any given situation, narrower and more stable confidence intervals can make a big difference in the quality and in the results obtained. This is especially important in the area of CT drug safety analysis, whereas the problem with small counts and multiple comparisons issues are very significant.

4. Appendices

4.1.   *Requests for the Collaborative Review*

Dr. Szarfman was asked by the DAIOP to support the following:

(1) Characterize the population that encompasses the 9 febrile neutropenia (FN) studies submitted to the Agency with the original supplement for this indication. The approval of the supplement presented at a public advisory committee meeting was on May 16, 1997. Per advice from Dr. Szarfman, DAIOP asked the sponsor to resubmit these data in the Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) standardized format.

(2) Search for any additional deaths, beyond those originally noted by the Applicant, which may have occurred among the patients enrolled in the 9 FN studies. This was necessary because neither the Clinical Trial (CT) data typically submitted to the FDA in a non standardized format, nor the CDISC SDTM format standards have a unique variable for death; and the Sponsor's numbers of deaths appeared to change from one submission to the next;

(3) Perform a reassessment of patient deaths and risk factors, including concomitant medications, and any adverse events that could be associated with the deaths, as well as associations between patient co-morbid conditions and death.

4.2. *The Cefepime Data*

4.3. *Why Analyze cefepime's Data in a Standardized Format?*

Even though CDER has made great strides in the analysis of CT data, making quick decisions about the safety of applications remains very challenging. This is in part because of the complexity surrounding why adverse reactions occur in humans, a lack of objective markers to link an adverse event to a drug, and fully mature and very comprehensive data standards for drug products submitted to the Agency.

Additionally, we do not use routinely standard analytical tools capable of identifying gaps in the data standards, of helping correct such gaps, and of assessing the corrected data in real time.

Data standards will allow CDER to gain in timeliness and accuracy. The data standards are of prime importance for CDER to access and review the data in a timely manner.

However, without hands-on testing the emerging data standards using real-life CT data, the process of refining and establishing comprehensive data standards for CT data will be delayed longer than needed.

The Agency expects an increase in publications/citizen petitions based on meta-analyses of public domain CT results. It is also often necessary to reanalyze CT data in light of new information about a particular adverse event or class of events for a drug or class of drugs months—or even years—after the initial analysis. With current ad-hoc methods, the prevalent use of non-standardized data and lack of automated review tools, the process of re-evaluation may take as long to perform as the original review.(5)

In many such situations, the Center will benefit from having ready access to standardized CT data and to standardized automated analytical tools.

4.4. *Why Use the MBLR Safety Data Mining Method?*

To help better deal with the issues described above and to assess the cefepime reported mortality imbalance, this reviewer collaborated with Dr. William DuMouchel and Sally Cassells from Lincoln

Technologies to help implement and test an R-based Bayesian module named MBLR incorporated into an automated analytical system.(11)

DuMouchel explained his new methodology in several presentations at the FDA, and clarified complex issues through several e-mail exchanges and telephone conversations with Dr. Ana Szarfman, and an e-mail exchange with Dr. Joy Mele (9). This reviewer summarized these discussions in Section 4.8.9.7 starting on page 73.

This new algorithm was implemented in conjunction with a set of other interactive analytical tools and graphic displays within the WebSDM CTSD software (7).

MBLR performs pooled-data meta-analysis of complete and corrected subject level data submitted in the SDTM CDISC format. The Industry with FDA participation developed SDTM CDISC. The SDTM CDISC format serves as a standard for representing patient-level clinical datasets.

The pooled analysis of complete and corrected subject level data converted into a common data standard with drill down capabilities to individual patient profiles and narratives is a great improvement over meta-analyses of secondary, published data.

The data mining of CT safety data has many of the same challenges as data mining of spontaneous reports. Although the data will be cleaner than spontaneous reports data, the problem with small counts and multiple comparisons issues are just as significant (9).

The MBLR method that we employed uses a Bayesian model that is capable of providing stable multivariate estimates associated with treatment for many possibly related adverse events; of searching for potential syndromes (different, but overlapping adverse events in the same patients); of searching for subgroup effects, and of borrowing strength across medically related adverse events.

This method helps guard against generating multiple false positive signals due to multiple independent comparisons and small counts, and helps control for both Type I (false positive) and Type II (false negative) errors in the analysis.

The SDTM CDISC data standards facilitate data pooling across CTs. The combined analysis of multiple studies using DuMouchel's newly created Bayesian models that correct for multiplicity and small counts is a form of pooled-data meta-analysis.(9)

With these tools, the process of analysis is explicit about assumptions and predictors, data selection, and inclusion/exclusion of studies, and the user can test the variation of the results under different scenarios to assess the model uncertainties.

All the results are hyperlinked to other representations of the data, including to Sector Maps or Patient Profile displays. These analytical functions give the clinical and statistical reviewer a deeper understanding of the complex, multivariate data analyzed.

The fully auditable functions, generated in a human-readable format (a format that most reviewers can comprehend) increase the ability of the reviewer to reflect on the data decisions that she/he made to generate results. These audit functions also enable the reviewer to identify and document data issues that require correction, to make or request informed data corrections, and to rerun previous MBLR runs in an automated fashion or rerun MBLR with updated information, all in real time.

The reviewer is then in a position to use corrected data early in the review process, instead of discovering these data errors as obstacles late in the review process.

4.4.1. *More Details about Patients and Methods*

Table 13: Gender distribution by treatment and study

Study	Cefepime					Comparator					Total		
	F	%	M	%	Total	F	%	M	%	Total	F	M	Total
CS ai411118	29	49.15	30	50.85	59	28	49.12	29	50.88	57	57	59	116
CS ai411131	46	44.23	58	55.77	104	33	36.67	57	63.33	90	79	115	194
CS ai411137	15	42.86	20	57.14	35	14	38.89	22	61.11	36	29	42	71
CS ai411186	111	45.87	131	54.13	242	48	43.24	63	56.76	111	159	194	353
CS ai411189	61	42.36	83	57.64	144	58	42.34	79	57.66	137	119	162	281
CS ai411198	24	44.44	30	55.56	54	18	31.58	39	68.42	57	42	69	111
CS ai411204	69	50.00	69	50.00	138	65	47.10	73	52.90	138	134	142	276
NC ai411143	39	46.43	45	53.57	84	0		0		0	39	45	84
NC ai411158	14	46.67	16	53.33	30	0		0		0	14	16	30
Total 9 Studies	408	45.84	482	54.16	890	264	42.17	362	57.83	626	672	844	1516

Note that these CTs, in general, studied a higher proportion of males regardless of treatment arm.

Table 14: Race distribution by treatment and study

Study	Cefepime									Comparator								
	Black	%	White	%	Other	%	NULL	%	Total	Black	%	White	%	Other	%	NULL	%	Total
CS ai411118	5	8	45	76	9	15	0	0	59	3	5	44	77	10	18	0	0	57
CS ai411131	6	6	78	75	20	19	0	0	104	12	13	63	70	15	17	0	0	90
CS ai411137	1	3	34	97	0	0	0	0	35	1	3	35	97	0	0	0	0	36
CS ai411186	0	0	0	0	0	0	242	100	242	0	0	0	0	0	0	111	100	111
CS ai411189	2	1	135	94	7	5	0	0	144	2	1	135	99	0	0	0	0	137
CS ai411198	0	0	50	93	4	7	0	0	54	0	0	53	93	4	7	0	0	57
CS ai411204	20	14	109	79	9	7	0	0	138	24	17	107	78	7	5	0	0	138
NC ai411143	1	1	70	83	13	15	0	0	84	0		0		0		0		0
NC ai411158	0	0	29	97	1	3	0	0	30	0		0		0		0		0
Total 9 Studies	35	4	550	62	63	7	242	27	890	42	7	437	70	36	6	111	18	626

Note that these CTs, in general, studied mostly Caucasian and that Study ai411186 did not collect data on race.

Study ai411204 included the highest proportion of blacks (14% with cefepime and 17% with comparator).

Table 15: Age distribution by treatment and study

Study	Cefepime						Comparator						Total					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
CS ai411118	59	49	17	50	19	86	57	52	18	52	21	80	116	50	17	50.5	19	86
CS ai411131	104	23	20	15	1	76	90	25	22	13	1	73	194	24	21	14.5	1	76
CS ai411137	35	43	8	44	27	60	36	41	11	42	19	58	71	42	10	42	19	60
CS ai411186	242	45	13	44.5	15	79	111	45	14	45	18	71	353	45	14	45	15	79
CS ai411189	144	51	15	55	20	86	137	49	18	51	16	88	281	50	17	52	16	88
CS ai411198	54	48	15	47	17	74	57	50	15	53	18	80	111	49	15	50	17	80
CS ai411204	138	53	15	54	18	82	138	56	15	59	19	81	276	54	15	57	18	82
NC ai411143	84	47	17	50	16	84	0						84	47	17	50	16	84
NC ai411158	30	37	10	39	18	53	0						30	37	10	39	18	53
Total 9 Studies	890	45	18	46	1	86	626	46	19	48	1	88	1516	45	18	47	1	88

Note that the age distribution across treatment groups and studies was similar, except for Study ai411131 that also enrolled pediatric patients

4.5.   *Data Requests and Analysis Process*

4.5.1. *Data Requests to the Sponsor*

This reviewer asked DAIOP to request that the sponsor provide the patient-level data in SDTM SDISC format. The sponsor provided the data for the 9 FN studies in these standards.

The specific instructions sent to BMS are described within the endnote #12.

4.5.2. *Data Submitted by the Sponsor*

The sponsor performed the data transformation process that included converting the CT data organized on a by study basis into a common SDTM SDISC standard format (13) converting the adverse event data into a common MedDRA version (11.0) and the laboratory results data into common standard units.

The data submitted on May 30, 2008 by the applicant were loaded into WebSDM with CTSD (14).to check for compliance with CDISC standards and for errors in the data before the formal analysis would start. The Patient Profile Data (PP) software was used to interactively assess the submission data and patient level, and TableTrans (TT) to correct critical data errors detected by WebSDM CTSD, and to integrate the data across all the MBLR runs.

4.5.3. *Data Problems that we Corrected*

4.5.3.1.   *Data Issues with Current SDTM CDISC Standards*

Some of the major gaps in the SDTM CDISC standards that we identified and corrected before pursuing with the analyses included a lack of a unique place for deaths, a lack of a consistent representation of exposure, and a lack of a unique representation of multiple episodes of treatment and of their corresponding baseline dates.

4.5.3.1.1. *Lack of a Unique Place for Recording Deaths*

The SDTM version 3.1.1 of CDISC used to transform the data for this review as well as the more current SDTM version 3.1.2 do not address the need for a unique place for recording deaths. Indeed, SDTM CDISC still contains several different places to record deaths for the following categories of deaths:

- Death as an outcome of an adverse drug event in the adverse event domain;

- Death as a category of a serious adverse drug event in the adverse event domain;

- Death as a reason for discontinuation in the disposition domain;

- Death as not being a reason for discontinuation in the disposition domain;

- Death described in the narratives of deaths and dropouts (no domain assigned yet).

Furthermore, a mortality report for a death that occurs after the subject discontinued from the study will not fit in any of these places. It is not uncommon for an adverse event that ends in death to be for a subject discontinued before the death occurred, apparently leaving the sponsor with no standard place to record the death and the date of death. The reviewer may find theses cases described within narratives.

SDTM CDISC still does not support a unique standardized place for recording the patients who died and the death details including date of death typically collected with a mortality report.

4.5.3.1.2. *Lack of a Standard for Representing Multiple Treatments and Baselines*

The start date of treatment and the treatment arm in the demographic table defines the baseline date and treatment arm.

Although some patients had up to 5 episodes of FN, the treatment arm in the demographic table submitted by the applicant was based on the first episode of FN.

In the original review of these studies completed on June 12, 1997, the reviewers Drs. David Ross (clinical reviewer) and Aloka Chakravarty (statistical reviewer) choose to assess the baseline and treatment arm of the first episode of FN.

4.5.3.2. *Inconsistencies in the Data Submitted*

4.5.3.2.1. *Unique Patient Identifier*

The unique patient identifiers in the narratives was represented as a VARCHAR2(13) [with a trailing space] and in the datasets as a VARCHAR2(12) [without a trailing space].

The different representation of unique patient identifiers across data resources precludes an adequate linkage of information across these data resources, if the problem is not detected and addressed.

4.5.3.2.2. *Exposure*

In all studies, except for study ai411204, the exposure data submitted in SDTM CDISC standards "one record" per dose per day (each with a start date, but not an end date) for each episode of FN.

In study ai411204, exposure had one record (a range with a start and end date) "for each episode" of treatment. SDTM CDISC does not specify the need for a consistent representation of exposure across all the studies.

4.5.3.2.3.   *Susceptibility*

The data for the microbiology and susceptibility domains were incorporated into PPs to understand potential patterns with the data.

Using these profiles we identified that the pathogens had susceptibility information on cefepime, but not on the comparator treatments.

4.5.3.2.4.   *Treatment Arms in Exposure*

In the EX domain EXTRT is represented in upper case in 8 studies and in Upper and Lower case in the remaining study.

4.5.3.2.5.   *Medical History Values*

Multiple free text phrase variations defined the same medical history (for example, acute leukemia)

4.5.3.3.   *How did we Address these Problems?*

4.5.3.3.1.   *Created a Consistent Representation of Unique Patient Identifiers*

We identified and removed a trailing space in the unique USUBJID of the narratives submitted by the applicant, so the narratives could be linked to the rest of the data.

4.5.3.3.2.   *Created Records for a New Preferred Term Named 'Death' in the AE (Adverse Event) Domain for each of the Patients who Died*

To perform an analysis of risk of death and risk factors associated with death we had to first identify all the patients who died from the several places in the data that they were stored (see 4.5.3.1.1.)

WebSDM CTSD was used to generate individual patient profiles for each of these patients linked to the sponsor's narratives about their deaths.

This process enabled Dr. Peter Kim, the primary clinical reviewer of this NDA supplement, to assess these patients. After his assessment was completed, a total of 141 unique subject identifiers (USUBJID) were found for patients who may have died during the course of the studies. Out of these 141 USUBJIDs, there were 11 duplicate USUBJID who were assigned to patients who were enrolled twice for two separate episodes of FN. Out of the 130 remaining patients, 16 died more than 30 days after EOT.

This left 114 unduplicated patients who died within 30 days of EOT.

The data re-submitted by the sponsor on August 28, 2008, was transformed to incorporate records with a newly created 'Death' adverse event as a PT for each of the 114 patients selected by Peter Kim as meeting his definition of death.

For two subjects who had no previous AE records, we created a new AE record containing the PT 'Death'.

The data transformation process was done by this reviewer using the TableTrans (TT) software, prior to reloading the data into the WebSDM CTSD. This reviewer received extensive technical support from Lincoln Technologies under a contract arrangement.

4.5.3.3.3. Requested that BMS Categorize the Susceptibility of the Pathogens to All Antimicrobials used in these Studies

The Division requested to BMS to resubmit the microbiology and susceptibility domains with complete information about the susceptibility of pathogens to all antimicrobials used in these studies.

The Division also asked BMS to add the specific pathogen being assessed as a new variable in the susceptibility datasets named BS.

BMS submitted the updated datasets for the BS domain on August 28, 2008.

The resubmitted datasets were not set up quite right to be used within WebSDM. The submitted BS domain data had to be split into two datasets (BS, SUPPBS). The Pathogen variable was included in the supplemental qualifier dataset ([15]).

At the end, this process facilitated the access to the microbiological data and the follow-up review of the cases by Peter Kim.

Peter Kim reviewed the data for the patients who died and had a resistant pathogen. Peter Kim concluded that in several cases it was unlikely that the resistant pathogen caused the patient's death for several reasons, including the presence of isolates classified as resistant that were contaminants, and patients that seem to have died from their serious co-morbid conditions.

4.5.3.3.4. Identified the Most Recent Episode of Treatment for Patients with More than One Episode of FN, Including the Valid Start Date for Defining Baseline

Patients could have received multiple episodes of treatment for FN, but the sponsor assigned the overall treatment to the first episode of FN.

However, we needed to assess the most recent episode of treatment for patients with more than one episode of FN, including the valid start date for defining baseline.

Therefore, for an analysis based on the most recent treatment assignment, we had to first identify in the exposure table the first and last date of each episode of FN. Second, we had to identify the corresponding treatments. Third, we had to use the first and last date of the most recent episode to recode the start and end date and the treatment in the demographic table.

As exemplified in Figure 23, we created new treatment names by concatenating the treatments used during the first and last episode of FN. For example, for analysis purposes, if cefepime was used during the first episode and ceftazidime during the last one, we named the treatment sequence as 'cefepime-ceftazidime' and assigned this patient to the comparator ceftazidime arm.

Figure 23 displays and links the laboratory domain data with the exposure data of a single patient. The x-axis depicts the same timeline for the data domains, and shows the number of days since the beginning of the most recent episode of FN. The y-axis depicts the label of each row in the laboratory and exposure domains. The treatments for each of the 3 episodes of FN are highlighted by yellow circles. Note that the baseline was reassigned by Ana Szarfman to the beginning of the last episode of FN

Figure 23: Graphic display of a patient level information to exemplify the reassignment of the baseline day and treatment to the day and treatment of the most recent episode of FN
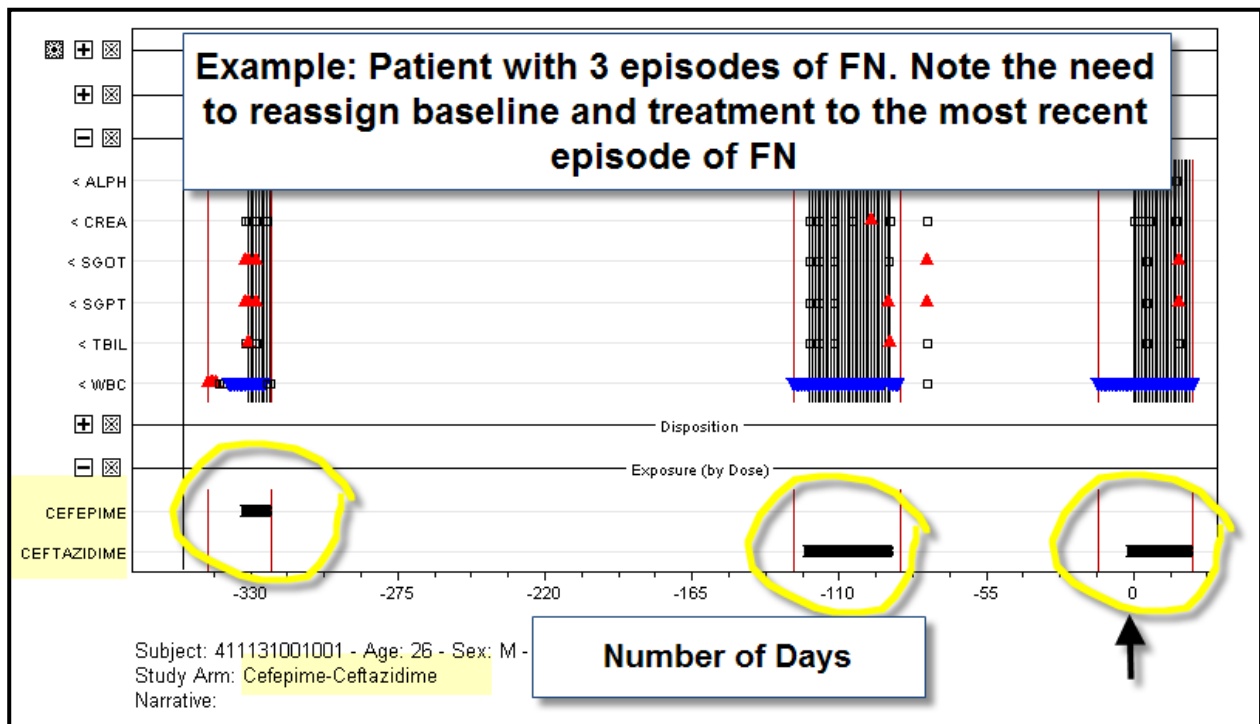
If only one episode of FN occurred, we analyzed the treatment and baseline assigned to each patient during the first episode (essentially the only episode).

4.5.3.3.5. *Created consistent Number of Variables Across Studies for Pooling Purposes*

To properly transform the CT data organized on a by study basis into a common SDTM SDISC standard format also requires the presence of a complete and consistent set of variables in each domain across all the studies, even for the variables with missing values.

In the cases where the applicant excluded variables from the studies with missing values, we added these variables (but not the values) to be able to avoid the problem of shifting columns when pooling data across multiple studies.

4.5.3.4. *MBLR Runs*

4.5.3.4.1. *Created Category Breakdowns for Data Pools and the MBLR Runs*

To consistently perform MBLR analyses across different data pools, we created category breakdowns using the largest pool of data. Table 16 is an audit trail of the grouping used for the covariates in the MBLR runs.

Table 16: Category breakdowns for the MBLR analysis

ID	Category Type	Name	Source Column	Categories
1289	Sex	Sex	SEX	F includes: 'F'; M includes: 'M';
1290	Race	Race	RACE	Other includes: 'H', 'O', 'X'; Black includes: 'B'; White includes: 'W';
1294	Medical History	Diabetes mellitus	MHTERM	Diabetes mellitus includes: 'DIABETES MELLITUS', 'Other: GLUCIDIC INTOLERANCE DIAGNOSED';
1295	Medical History	Renal impairment	MHTERM	Renal impairment includes: 'Other: LOW GRADE RENAL INSUFFICIENCY', 'Other: IMPAIRED KIDNEY FUNCTION', 'Other: NON-FUNC L/KIDNEY';
1300	Concomitant Medication	Bone marrow transplant	CMCAT	Bone marrow transplant includes: 'Bone Marrow Transplant';
1297	Dosing	Arm of first randomization	ARM	Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime'; Comparator includes: 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';
1298	Dosing	Arm of last randomization	ARM	Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime'; Comparator includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';
1299	Concomitant Medication	Anti-microbial medication	CMCAT	Antimicrobial medication includes: 'Concomitant Antimicrobial Medication', 'Post Study Antimicrobial Therapy';
1301	Concomitant Medication	Surgical procedure	CMCAT	Surgical procedure includes: 'Concomitant/Post Therapy Surgical Procedures';
1302	Indication	Study	STUDYID_	CS ai411118 includes: 'CS ai411118 FN LE (ai411118)'; CS ai411131 includes: 'CS ai411131 FN LE (ai411131)'; CS ai411186 includes: 'CS ai411186 FN LE (ai411186)'; CS ai411137 includes: 'CS ai411137 FN LE (ai411137)'; CS ai411189 includes: 'CS ai411189 FN LE (ai411189)'; CS ai411198 includes: 'CS ai411198 FN LE (ai411198)'; CS ai411204 includes: 'CS ai411204 FN LE (ai411204)'; NC ai411143 includes: 'NC ai411143 FN LE (ai411143)'; NC ai411158 includes: 'NC ai411158 FN LE (ai411158)';
1430	Medical History	Lymphoma/multiple myeloma	MHTERM	Key MHs includes: 'MALIGNANT LYMPHOMAS', 'NON-HODG LYMPHOMA,MULT MYELOMA', 'Other: CHEMOTHERAPY FOR MALIGNANT LYM', 'MULTIPLE MYELOMA', 'MDS + MULTIPLE MYELOMA';
1431	Medical History	Solid tumor	MHTERM	Solid tumor includes: 'ALIMENTARY TRACT CANCER', 'BREAST CANCER', 'CANCER OF ENDOCRINE GLANDS', 'CANCER OF UNKNOWN ORIGIN', 'LUNG CANCER', 'MALE GENITAL CANCER', 'Other: CANCER PAIN', 'Other: CHRONIC CANCER PAIN', 'UROLOGIC CANCER', 'BONE TUMORS', 'CENTRAL NERVOUS SYSTEM TUMORS', 'HEAD AND NECK TUMORS', 'Other: SOLID TUMOR OF THE RENAL PAREN', 'Other: YOLK SAC TUMOR', 'TUMORS OF FEMALE REPR.ORGANS', 'TUMORS OF THE EYE', 'MALIGNANT MELANOMA', 'NEUROBLASTOMA', 'Other: NEUROBLASTOMA', 'SOFT TISSUE SARCOMA', 'Other: ADENOCARCINOMA OF UNKNOWN PRIM', 'Other: SQ CELL CARCINOMA ANAL CANAL', 'UNDIFFERENTIATED CARCINOMA (ME', 'Other: METASTATIC LESION BEHIND RIGHT', 'CA OF MAJOR DIGESTIVE GLANDS', 'Other: NEOPLASTIC DISEASE';

ID	Category Type	Name	Source Column	Categories
1432	Medical History	Acute leukemia	MHTERM	Acute leukemia includes: '10.92 ACUTE MYELOID LEUKEMIA', '5.12.92 ACUTE MYELOID LEUKEMIA', 'ACUTE BIPHENOTYPIC LEUKAEMIA', 'ACUTE MEYLOID LEUKEMIA', 'ACUTE MYCLOBLASTIC LEUKEMIA M1', 'ACUTE MYCLOID LEUKEMIA', 'ACUTE MYELOBLASTIC LEUCEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA M1', 'ACUTE MYELOBLASTIC LEUKEMIA M5', 'ACUTE MYELOGENOUS LEUKEMIA', 'ACUTE MYELOGENOUS LEUKEMIA M2', 'ACUTE MYELOGENSUS MYELOIC LEUKAEMIA', 'ACUTE MYELOID LEUCAEMIA', 'ACUTE MYELOID LEUCEMIA (RABM3', 'ACUTE MYELOID LEUKAEMIA', 'ACUTE MYELOID LEUKAEMIA (M1)', 'ACUTE MYELOID LEUKAEMIA (M7)', 'ACUTE MYELOID LEUKAEMIA - MI', 'ACUTE MYELOID LEUKAEMIA M5', 'ACUTE MYELOID LEUKEMIA', 'ACUTE MYELOID LEUKEMIA (AML M1', 'ACUTE MYELOID LEUKEMIA (HYPER', 'ACUTE MYELOID LEUKEMIA (M3)', 'ACUTE MYELOID LEUKEMIA (MX)', 'ACUTE MYELOID LEUKEMIA M2', 'ACUTE MYELOID LEUKEMIA SINCE 1', 'ACUTE MYELOID LEUKEMIA ST POST', 'ACUTE MYELOID LEUKEMIA,TYPE M5', 'ACUTE MYELOIDE LEUKEMIA', 'ACUTE MYLEOID LEUKAEMIA', 'ACUTE MYLOID LEUKEMIA', 'AML-ACUTE MYELOGENOUS WITH MONOCYTIC SUBTYPE', 'LMA NY/ACUTE MYELOID LEUKAEMIA', 'MACUTE MYELOID LEUKEMIA VERY', 'MYLEODYSPLASTC DISORDER EVOLVING INTO ACUTE LEUKEMIA', 'RELAPSED ACUTE MYELOIDLEUCHEMI', 'AML', 'AML - M3', 'AML - M5', 'AML - M5A', 'AML - MSQ DIAGNOSED 11/92', 'AML AFTER MDS-RAC-T, NOW RELAP', 'AML DIAGNOSED 060593', 'AML DIAGNOSED 2/92,NOW 2ND REL', 'AML FAB M3', 'AML M1', 'AML M3', 'AML M4', 'AML M5', 'AML M5A', 'AML OF M4-M5SUBTYPE', 'AML RELAPSE', 'AML SEC TO MYELOPROEIFERATIVE', 'AML SINCE 7/92 AFTER MOS (TY', 'AML, TYPE PROMYELOID', 'AML-M2', 'AML-M2 WITH TRANSLOCATION', 'AML-M5A', 'AML-MS DIAGNOSED 1/93', 'AML-MSA', 'MDS-AML', 'RAEB-T -> AML', 'AC MYELOID LEUKEMIA', 'LEUKEMIA : ALL', 'LEUKEMIA : ANLL', 'BLASTIC TRANSFORM OF MYELODYSP', 'MYELODYSPLASTIC SYNDROME IN BL', 'ACUTATIVE OF CHRONIC MYELOMONO';
1490	Indication	Cefepime vs Ceftazidime Studies	STUDYID_	ai411131 includes: 'CS ai411131 FN LE (ai411131)'; ai411189 includes: 'CS ai411189 FN LE (ai411189)'; ai411204 includes: 'CS ai411204 FN LE (ai411204)';
1748	Dosing	Reversed arms	ARM	Treatment includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin'; Comparator includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime';
611	Age	Age	AGE	<=17 <= 17.0; 17.0 < <=40 <= 40.0; 40.0 < <=60 <= 60.0; 60.0 < >60;
632	Baseline Lab	Creatinine (2)	LBSTRESN	<=2.5 <= 2.5; 2.5 < >2.5;
790	Baseline Lab	Neutropenia (3)	LBSTRESN	<=100 <= 0.1; 0.1 < <=500 <= 0.5; 0.5 < >500;

4.6.　　　*Web Submission Data manager (WebSDM)*

This section extracted descriptions from the WebSDM software package.

WebSDM (Web Submission Data Manager) is a web-based system that is designed to work with clinical trial data submitted to the Food and Drug Administration (FDA) consistent with the CDISC electronic submission data standards.

WebSDM enables to:

Verify that the-provided case report data conforms to the CDISC Study Data Tabulation Model (SDTM). The checking process checks the metadata and clinical data for compliance with CDISC standards; some checks are built-in and some are added as rules (edit checks) by users with appropriate permissions.

View summary and detailed clinical data and metadata for domains in practical formats for review and export.

Query the study data by specifying variable-based criteria and save lists of subjects meeting those criteria.

Define and run summary and detail reports based on study data. See About Reports.

For most activities in WebSDM, the reviewer must select an application (that is, a submission) and study or study pool to use.

An application may contain multiple studies. Each study has multiple domains. A domain is a collection of data observations with a topic-specific commonality about clinical subjects; for example, demographics information or adverse events. WebSDM domains correspond to CDISC data domains.

4.7. *Clinical Trial Signal Detection (CTSD)*

This section extracted descriptions from the WebSDM software package.

WebSDM contains CTSD, which supports the detection and evaluation of possible safety issues in the clinical trial data. Using CTSD, you can do the following:

- Perform screening analysis, which generates statistical scores for associations of a treatment group (as compared to a comparator group) and issues. The "issue" depends on the type of analysis. For example, for a MedDRA PT disproportionality analysis, the issue is a particular adverse event Preferred Term (PT), and for a clinically significant lab analysis, the issue is a particular lab result.

- Identify issue clusters, which are sets of three or more issues that tend to co-occur more for subjects in the treatment group than for subjects in the comparator group. Issue cluster mining identifies clusters (or sets) of issues that co-occur under treatment more often than the occurrence rates for the component individual issues under treatment would lead one to expect.

- Create potential signals, which are collections of screening analysis results, issue clusters, and documents.

- Perform Bayesian logistic regression on a potential signal to generate statistics indicating how issues attached to the potential signal are related to treatment, and which subgroups (based on covariates such as age or sex) may be interacting with treatment.

4.8. *The MBLR Method*

The following sections summarize descriptions provided by William DuMouchel.(9)

4.8.1. *Bayesian Shrinkage Models*
- Statistical validity of searching for extreme differences
    - Most significant adverse event or patient subgroup
- Classical approach to post-hoc interval estimates
    - Maintain centers of CI at observed differences
    - Expand widths of every CI
    - Expansion is greater the more differences you look at
    - If you look at too many, the CI's are too wide to be useful
- Bayesian approach
    - Requires a prior distribution for differences
        - Can estimate it from the multiple observed differences available
    - Centers of CI's are "shrunk" toward average or null difference
        - High-variance differences shrink the most
    - Widths of CI's usually shrink a little too
    - The more you look at, the better you can model the prior distribution

4.8.2. *Searching for Event Clusters*

- An event cluster (associated with treatment) is a set of at least three adverse events (AEs) for which all pairs of said AEs tend to show up in Treatment patients more often than Comparator patients and also more than expected if the AEs are independent within each arm of the study
  - Defining potential syndromes by event frequency distributions rather than by theoretical medical mechanisms
- We declare a potential syndrome if all pairs within a cluster meet some distributional threshold
  - Syndromic Odds Ratio for 2 events (Treatment vs. Comparator)
    - $SOR(E1, E2) = OR(E1*E2)/max[OR(E1), OR(E2), 1]$
  - Bayesian statistical methods estimate smoothed probabilities for AEs and pairs of AEs for each arm of the studies
    - EB versions of Beta-binomial model seem to work well
  - Clustering algorithms find groups of events having high SORs

4.8.3. *Empirical Bayes Beta-Binomial Model*

- Assume K different binomial distributions
  - $N_k \sim$ Binomial(n_k, P_k) $k = 1, ..., K$
  - $P_k \sim$ Beta(bX_{k1}, bX_{k2}) N, n, X known; P_k unknown
- Suppose you want to shrink N_k/n_k toward $X_{k1}/(X_{k1} + X_{k2})$
  - Estimate b by maximum likelihood for beta-binomial distribution
  - Only one parameter to estimate
  - Posterior mean of $P_k = (N_k + bX_{k1})/(n_k + bX_{k1} + bX_{k2})$
- Various choices of X for different applications
  - $X_{k1} = p0, X_{k2} = 1 - p0$ [Shrink every N_k/n_k toward p0]
- The shrinkage estimators are useful when many of the counts are 0 and you want to estimate odds ratios
  - Multiple comparisons protection when searching for extreme deviations

4.8.4. *Bayes Model for Event Probabilities*

- Events 1 to K with Treatment and Comparator Groups
  - nt patients in treatment group, (n – nt) in comparator group
  - N_{kt} treatment patients with event k, $(N_k – N_{kt})$ in comparator group
  - P_k = probability of event k in treatment group [= N_{kt} / nt ??]
  - Q_k = probability of event k in comparator group [= $(N_k-N_{kt})/(n-nt)$??]
  - Bayes model shrinks both P_k and Q_k toward N_k / n
  - Equivalently, shrink every N_{kt}/N_k toward nt/n
  - "Beta-binomial" Bayesian model for proportions
  - $P_k = (N_{kt} + bnt/n) / (N_k + bnt/N_k)$ [estimate b by EB method]
  - $Q_k = (N_k - N_{kt} + b (n-nt)/n) / (n-N_k + b(n-nt)/N_k)$ [same b for all k]
- Odds Ratios $OR.EB_k = P_k(1 – Q_k) / Q_k(1 – P_k)$
  - 90% confidence intervals $(OR.05_k , OR.95_k)$

4.8.5. *Bayes Model for Event Pairs*

- N_{jk} = Number of patients with both AE j and AE k
  - N_{jkt} and $(N_{jk} – N_{jkt})$ in treatment and comparator groups
  - P_{jk} = probability of both event j and k in treatment patient
  - Q_{jk} = probability of both event j and k in comparator patient
  - If AEs are independent, $P_{jk} = P_jP_k$ and $Q_{jk} = Q_jQ_k$

- o Another beta-binomial model to shrink Njkt/nt toward PjPk and yet another to shrink (Njk – Njkt)/(n – nt) toward QjQk
- Odds Ratios for AE pairs
  - o ORjk = Pjk(1 – Qjk) / Qjk(1 – Pjk)
- Syndromic Odds Ratio
  - o SORjk = ORjk / max(1, ORj, ORk)
  - o AE pairs occur together preferentially in treatment group more strongly than can be explained by single-AE associations

4.8.6. *Logistic Regression for Subgroup Analyses of Multiple Events*

- Start from a set of Medically Related events to study
  - o Set of events from potential signal
  - o Set of events from SOR clusters (potential syndromes)
  - o Set of ad-hoc events, or all events within a MedDRA SOC
- Fit Logistic Regressions to each AE as a response
  - o Use exactly the same predictor model for each AE
    - Age, gender, concomitant medication, medical history, etc.
  - o Include treatment and interactions with treatment as predictors
  - o Generate parameter estimates for predictors and interactions
- Empirical Bayes shrinkage of estimated coefficients
  - o Coefficients of each predictor borrow strength across AEs
  - o Overall treatment and interaction effects shrink toward 0

4.8.7. *Rationale for EB Model Across Events*

- Coping with fine grain of adverse event data
  - o Compare T vs. C on 20 varieties of hepatic issues
  - o Approach 1—separate analyses of all 20 events
    - Small counts lead to non significant comparisons
    - Adjustment for multiple comparisons further reduces sensitivity
  - o Approach 2—define a single event as union of the 20 events
    - Significant differences may be washed out by the pooling
    - Even if significant, little information about original 20 differences
- Compromise approach—EB hierarchical model
  - o 20 individual estimates that "borrow strength" from each *other*
  - o Let Bjk = coefficient of jth treatment effect/interaction on kth AE
    - Bjk ~ N(mj, sj2)   [prior distribution shrinks AEs toward each other]
    - mj ~ N(0, t2)   [prior for overall treatment effects shrinks toward 0]
  - o Estimated prior variances sj2 and t2 control amount of shrinkage
    - Appropriate amount of shrinkage avoids multiple comparisons fallacy

4.8.8. *Display of Subgroup Effects*

- Logistic Regression Coefficients Are Interpreted as Logs of Odds Ratios
  - o Graphs of confidence intervals for each subgroup
  - o Confidence intervals that do not overlap are interpreted as significant differences in subgroups
- Separate graph for each covariate and AE
  - o Different layouts possible
  - o Compare original and shrinkage estimates
  - o Compare overall treatment effects across AEs
  - o Compare subgroup effects across medically related AEs

4.8.9. *Follow-up Comments by Dr. William DuMouchel*

The following comments by DuMouchel were made to answer questions from Drs. Joy Mele and Ana Szarfman from CDER.

4.8.9.1. *Logistic Regression Estimates for Death*

The logistic regression estimates the log odds of death/no death as a function of predictors.

4.8.9.2. *Shrinkage*

If there are, say, 3 response variables (for example, death, cerebral bleeding, hypotension) and thus 3 sets of unadjusted coefficients, then the shrinkage estimate for each coefficient is a weighted average of four values: the value 0 plus the three unadjusted values. The weights depend on Bayesian theory and the coefficients and standard errors and correlations among the coefficients. And the corresponding unadjusted coefficient gets the greatest weight for the corresponding Bayesian coefficient.

4.8.9.3. *Comparator Arm MBLR Graph and Table*

The analysis describes how the probability of death depends on age, gender, and any other covariates.

When there are multiple covariates, the model-based estimate assumes that the effects on log odds are additive across covariates.

The results are the same as if we just took the comparator data and used logistic regression to predict death as a function of covariates. All covariates are assumed categorical. Instead of leaving out one category for each covariate as is often done with regression models, the coefficients of the LR are estimated under the constraint that they add to 0 across the categories of each covariate. When there are only two categories, such as sex female/male, solid tumor yes/no, etc, that means that one coefficient is the negative of the other. If there are 4 age categories, there will be 4 coefficients that sum to 0.

To get the predicted odds ratio for comparing death rates (or other items) for any two categories, the program subtracts the two coefficients, then takes the exponential of the difference.

If we are looking at odds ratio columns or scales in the figure (where we are already on the exponentiated scale rather than the log scale of the coefficients) the odds ratio for comparing any two categories is found by dividing the two values in the table or graph.

4.8.9.4. *Single "OR" in the MBLR Graph or Table*

The interpretation of a single "OR" in the table or graph would be to the average of the categories. Eg, males compared to the average of males and females. Each age group is the comparison of that group to the average of all age groups analyzed. Since this average is a synthetic concept, it is easier to focus on any pair of groups and imagine that the ratio of the given odds ratios predicts the two by two table of death versus those two age groups.

4.8.9.5. *Comparing Treatment to Comparator*

For the graph which focuses on comparing treatment to comparator (not merely describing the treatment arm), the values are scaled to cluster around the "overall" estimate of treatment to comparator.

The treatment/comparator odds ratio for females times the treatment/comparator odds ratio for males equals the square of the overall treatment odds ratio.

Similarly, the four age group treatment/comparator odds ratios average to the overall odds ratio (on the log scale).

If there was a significant age effect in the comparator-only analysis, but not in the treatment-interaction analysis, it means that an analysis of the treatment arm only subjects would probably show a similar age effect as the comparator only subjects, i.e., no difference between treatment and control.

Thus each odds ratio in this table or graph is the predicted treatment/comparator odds ratio for death/no death if the trial had been focused on that particular subgroup.

Of course like all subgroup analyses, there is a multiple comparisons problem when we look for the subgroup with the largest or smallest effects. The Bayesian versions of the table and graph use shrinkage estimates to discount or reduce these estimated effects.

4.8.9.6. *Widths of CI*

Answering why the widths of the comparators are narrower than the widths of treatment-comparators: The widths of CI are complicated functions of the entire design of the trial. But in general, there is more random error in comparing two things than in measuring just one of them, because there are two sources of error in the former.

4.8.9.7. *MBLR Answer When Selecting Only One Response.*

At the end of January 2009, William DuMouchel computed the EB answer for LR when there is only one response.

In an e-mail to Ana Szarfman, William DuMouchel described that the code is still preliminary and not vetted for quality control yet.

Some comments by DuMouchel, both general and specific:

Generally, EB models are more reliable the more data goes into them. When there is only one response, the assumptions behind the Bayesian model are harder to verify and so it is harder to know how much to trust the results. The main unknown issue is how much to shrink the coefficients toward 0, or, equivalently, how much to shrink the odds ratios toward 1. Having several responses provides a better guide for how much to shrink, although even then we still have the uncertainty as to whether we combined the right responses together.

Again, because more data in an EB model is better, the EB model with a single response is especially tenuous when there are very few predictors. DuMouchel described that he would be much less likely to trust an EB model if there were only treatment plus a single covariate like age, having only 5 or 10 coefficients in total.

He also stated that it is not fair to only select predictors (or responses) that were significant in a previous run. The shrinkage calculations should be based on the initial most medically plausible predictors.

DuMouchel stated that specifically looking at the results for these data that the single-response EB model shrinks all the odds ratios and their confidence limits almost to the null hypothesis value of 1. This happens because all but two of the unadjusted odds ratios (two age groups in the comparator arm) are very close to 1, so the method that he has implemented decides that there is virtually no evidence against the global null hypothesis and shrinks a lot.

DuMouchel also stated that it seems probable to him that he may have "over-shrunk" and that he cannot be so certain that all odds ratios are so close to 1 as the Bayesian confidence intervals would suggest. He stated that he could perhaps tweak the method so that such radical shrinking is prevented. DuMouchel will have to think more about that.

DuMouchel also stated that on the plus side, this potential over-shrinking makes false alarms less likely and is a form of multiple comparisons control.

DuMouchel also commented that if a reviewer can find more responses that are plausible to combine into a single MBLR analysis, the analysis method currently used will have more reliable estimates of how much to shrink.

Perhaps the best summary for these data is that based on the death outcome alone, the Bayesian analysis finds no differences, but combined with other markers of morbidity the analysis does suggest small effects even in the death rate.

4.8.10.   *Summary*

MBLR is a LR procedure that fits a special hierarchical model designed for the situation of multiple, but medically related, response variables in a two-armed trial or set of trials whose data have been pooled

The predictors must all be categorical. If a non-treatment predictor has K categories, rather than estimate just K-1 coefficients by leaving out one category, K coefficients are estimated under the constraint that they sum to 0

Exactly the same predictors are used for each response

For every non-treatment predictor in the model, the treatment interaction with that predictor is automatically also included in the model. This allows the estimation of separate treatment effects within subgroups defined by the other predictors

The estimates of each response analysis "borrow strength" from the estimates of the other response analyses. For every term in the model, the coefficients of the same term across responses are shrunk towards each other and also shrunk towards 0, according to empirical Bayes theory and estimates of certain variance components

If the estimates across responses are in close statistical agreement, the borrowing strength aspect can provide additional power compared to the separate non-Bayesian regressions. On the other hand, if these estimates differ significantly, the shrinkage towards 0 will provide conservative effect estimates that can be interpreted as an adjustment for multiple comparisons.

This hierarchical Bayesian model could be reformulated as a non-Bayesian random effects model, where the response-by-predictor interaction terms would be viewed as random effects.

4.9. *Loading Study Data and Production of Data Pools*

WebSDM CTSD was used to load each individual study data and to integrate the study data into several different data pools, including the following data pools:

The 7 comparative studies

The 2 non-comparative studies

The 3 single cefepime v ceftazidime studies.

All 9 studies

Figure 24: Details of the studies loaded and data pools generated

4.10. *Studying Potential Signals in WebSDM CTSD*

The following was extracted from the descriptions in the software package

4.10.1. *Potential Signals*

A potential signal in WebSDM CTSD is a collection of information that could indicate a drug safety concern, and thus is intended for subsequent statistical and medical evaluation. Potential signals can include results from any studies in a particular application. The reviewer can continue to add information to a potential signal over time. The following information can be added to a potential signal as supporting evidence:

- Issues from screening analysis results or issue clusters for any study in the application

- MBLR runs that have been performed for the potential signal

- Supporting documentation

- Annotations of the above components

- Comments about the potential signal

Typically, a potential signal is first created when a concerning issue or issue cluster is found by a reviewer of screening analysis results or issue cluster mining results. Information is then added to the potential signal as the signal goes through stages of medical and statistic evaluation. A MBLR run can be performed to determine the statistical significance of issues in the potential signal.

Each potential signal has a status, which is intended to provide information about the current position of the potential signal in the CTSD workflow, as well as control which activities can be performed with the signal.

4.10.2. *Cluster Mining*

An issue cluster is a set of three or more issues that tend to co-occur more for subjects in the treatment group than for subjects in the comparator group. Issue cluster mining identifies clusters (or sets) of issues that co-occur under treatment more often than the occurrence rates for the component individual issues under treatment would lead one to expect.

Issue cluster mining is based on a comparison of Empirical Bayesian adjusted odds ratio statistics for pairs of issues and the treatment drug.

When a cluster mining run has completed, the reviewer can view issue cluster results as heatmaps or confidence interval graphs and save relevant issue clusters. Once an issue cluster has been saved, the reviewer can add it to a potential signal, causing the individual issues in the cluster to be added to the potential signal as supporting results. The reviewer can the perform a Bayesian logistic regression analysis for issues in the potential signal.

Generally, cluster analysis is an exploratory technique. The clusters obtained differ depending on the algorithm and configuration options selected, and there are no clearly objective criteria for determining which solution is most informative. It is up to the analyst to determine if a cluster solution "makes sense".

4.10.3. *MBLR*

The results of an MBLR run for a potential signal provide information about how issues attached to the potential signal are related to treatment, and which subgroups may be interacting with treatment. Subgroups are based on predictors (covariates) of interest, such

as age group, sex, or medical history. The review of logistic regression results may support any of the following conclusions:

The issue appears related to treatment in a screening analysis, but is not related to treatment when covariates are included in an MBLR run, and these covariates show a strong relationship to issue outcome. This indicates that a randomization error may have occurred.

The issue is associated with treatment, and that association is affected by covariates. For example, smokers over age 65 may be more vulnerable to experiencing the issue.

The issue is associated with treatment, and that association is fairly constant across the set of tested covariates.

The statistics resulting from MBLR provide information about how a potential signal relates to the treatment drug for a particular study. Typically, the reviewer would perform MBLR analysis across multiple studies (that is, for a study pool).

4.10.3.1. *Compound Issues*

Simply including the set of individual issues that resulted from a cluster mining run does not test hypotheses specific to the cluster itself; such an approach would only test hypotheses about the individual items and their correspondence to the other factors in the regression (treatment and one or more predictors).

An issue cluster is found on the basis of greater than expected co-occurrence among its member issues for subjects in the treatment group. This implies that a subject with any two of the member issues "experienced" the cluster as far as cluster mining is concerned. To test logistic regression hypotheses about the relationship of the issue cluster to other predictors, a compound issue must be created.

A compound issue is an issue that the reviewer has defined as occurring if a specified set of conditions are met; the conditions can be joined by the SQL logical operators AND and OR. By default, a compound issue identifies subjects who experienced any two of the issues in the cluster. However, the reviewer may want to specify more complex criteria. For example, the reviewer might specify that Syndrome X exists if at least three of the 4 PTs "Abnormal dreams," "Anxiety," "Neuralgia," or "Sleep Disorder" occurred and Depression did not occur. A compound issue is necessary to test hypotheses about the issue cluster itself; individual issues from the cluster may be included in the MBLR run as well, but tests corresponding to such issues would be specific to these issues, not the cluster itself.

In contrast to clusters generated by an issue cluster mining run, compound issues are generated by the analyst and should be informed by medical knowledge and theory. Compound issues based on lax combinatorial criteria using issues collected only because of their relationship to treatment will produce statistically significant results of questionable validity.

4.10.3.2. *Automatic Screening*

Automatic screening is a process whereby CTSD generates the complete set of issues available for MBLR of a potential signal, as well as for issue cluster mining. The only statistic

generated by automatic screening is a count of subjects for whom each issue occurred. For MBLR, CTSD uses the automatic screening results to determine if issues attached to the potential signal from other studies are also available in the currently selected study. MBLR can reference issues from other studies only if they also exist in the currently selected study.

4.10.3.3.   *Configuring/Running MBLR*

To configure an MBLR run for a potential signal, the reviewer must specify predictors and issues. Predictors are the covariates, for example, subject characteristics or concomitant medications, used in the logistic regression run. To specify a predictor, the reviewer either selects from an existing category breakdown or create a new one. Responses are the issues or compound issues used in the logistic regression.

Analysis results from any study in an application may be attached to a potential signal.

The reviewer can select a dosing category breakdown to determine the treatment and comparator groups for the MBLR run. The reviewer can select a category breakdown for at least one predictor.

For the Age, Sex, and Race predictors, the reviewer can select only one category breakdown. For other predictors, the reviewer can select multiple category breakdowns by holding down the Ctrl key while the reviewer clicks the breakdowns.

To specify the issues or compound issues that the reviewer wants to include in the logistic regression, the reviewer selects appropriate checkboxes. The available issues include the following:

> Issues from screening analysis results that have been attached to the potential signal (except results of the following analysis types: Subject Disposition, Lab Change from Baseline, Vitals Change from Baseline, or a Custom MedDRA Query or any other custom analysis type)

> Issues that were attached automatically to the potential signal because an issue cluster was attached

> Compound issues that have been created for the potential signal

Currently, the selection of only one issue, can be done only for unadjusted results. However DuMouchel is working on a solution.(see page 73 of this review)

Optionally restrict the logistic regression to issues that occurred within a specified range of study days. The user can specify an "after Study Day __ " value, a "before Study Day __" value, or both. This does not restrict subjects; subjects who experience an issue only before or after the range of study days are counted as not experiencing the issue.

CTSD derives the relative day using the RFSTDTL_ variable in the DM domain and the appropriate __DTL_ variable from the domain used by the analysis type. The algorithm that computes the relative day first truncates the time components of the involved dates. In accordance with the SDTM guidelines, there is considered to be no Day 0.

There are <number-of-predictor-categories> predictor levels and 2 dose levels for <number-of-subjects> subjects. At least 10 subjects required for each level: If less than 10 subjects the analysis cannot be run.

MBLR analysis requires a minimum number of subjects to run. This number is equal to the number of categories (including the two dosing categories) multiplied by 10. For example, if the reviewer uses a category breakdown for sex (where there are two categories, Male and Female), the minimum number of subjects required is 40.

4.10.3.4. *Viewing MBLR Results*

The results of a Bayesian logistic regression run list the issues included in the run and allow the reviewer to view a graph or table of the results for individual issues or all issues.

Both standard logistic regression results and empirical Bayesian adjusted results are presented.

The reviewer can drill down from the tables and graphs results to the individual cases.

4.11. *Additional Results*

4.11.1. *Shrunken Odds Ratio Statistic for Deaths*

CTSD computes a "shrunken" odds ratio (16). The shrunken odds ratio is shrunk towards an OR of 1. This shrinkage leads to a more stable estimate of the OR when A and B are small or one of them is zero.

In the next two tables we describe the shrunken OR values for the PTs in the pool of pool of the 3 cefepime vs. ceftazidime single drug studies.

Note that cefepime seems to be more likely to be associated with bleeding events, dizziness, and hypotension (Table 17). Except for vaginal bleeding, these types of episodes were not found within the top OR values for cefepime vs. cefepime in the pool of the 3 cefepime-ceftazidime studies (Table 18).

Table 17: Top 20 Shrunken Odds Ratios more likely to be associated with the *cefepime* treatment than with ceftazidime in the subset of patients who died (Screening run 303)

MedDRA PT for subset = 'Death'	A	B	C	D	Shrunken OR
Dizziness	3	0	35	29	4.213
Petechiae	3	0	35	29	4.213
Acute respiratory distress syndrome	2	0	36	29	3.088
Arrhythmia	2	0	36	29	3.088
Cardiac arrest	2	0	36	29	3.088
Cyanosis	2	0	36	29	3.088
Cough	2	0	36	29	3.088
Cerebral haemorrhage	2	0	36	29	3.088
Haemoptysis	2	0	36	29	3.088
Oral disorder	2	0	36	29	3.088
Somnolence	2	0	36	29	3.088
Mouth haemorrhage	2	0	36	29	3.088
Stomatitis	4	1	34	28	2.29

MedDRA PT for subset = 'Death'	A	B	C	D	Shrunken OR
Hypotension	10	4	28	25	2.026
Agitation	1	0	37	29	2.019
Asthenia	1	0	37	29	2.019
Anorexia	1	0	37	29	2.019
Blood urine present	1	0	37	29	2.019
Candidiasis	1	0	37	29	2.019
Death	38	29	0	0	1

Table 18: Top 20 Shrunken Odds Ratios more likely to be associated with the *ceftazidime* treatment than with cefepime in the subset of patients who died (Screening run 232)

MedDRA PT for subset = 'Death'	A	B	C	D	Shrunken OR
Hypertension	4	0	25	38	5.491
Rales	4	0	25	38	5.491
Vaginal haemorrhage	3	0	26	38	4.254
Abdominal distension	5	1	24	37	3.825
Arthralgia	2	0	27	38	3.101
Breath sounds abnormal	2	0	27	38	3.101
Decreased appetite	2	0	27	38	3.101
Neurotoxicity	2	0	27	38	3.101
Oliguria	2	0	27	38	3.101
Sinus congestion	2	0	27	38	3.101
Wheezing	2	0	27	38	3.101
Vulvovaginal mycotic infection	2	0	27	38	3.101
Pruritus	2	0	27	38	3.101
Oesophagitis	2	0	27	38	3.101
Depressed level of consciousness	2	0	27	38	3.101
Cholecystitis	2	0	27	38	3.101
Headache	4	1	25	37	3.081
Jaundice	4	1	25	37	3.081
Tachypnoea	4	1	25	37	3.081
Death	29	38	0	0	1

4.12. *Time to Death in the 9 FN studies*

4.12.1. *Kaplan-Meier Survival Curves*

The following figures show the survival curves for the subset of patients who died.

Overall, the median survival across all 9 studies was similar: 20 days for cefepime and 18 days for the comparator (Figure 25). However, cefepime deaths tended to occur earlier in the beginning of the treatment or later than comparators in the end of the observation period (page 80).

Note that the confidence bands around survival curves for all patients who died show no significant difference between arms, and for the analyses by study. The analysis in females, by race, by age, and in patients who died with and without the covariates AL, AMM, BMT, and ST show similar findings. (see next figures).

Study ai411204, that had the highest proportion of cefepime deaths, had a median survival for cefepime of 22 days vs. 12 for the comparator. The 95% CI displayed as shaded areas for treatment arms merge into one area in each of the survival curves, except at the very end of the observation in males with a p value of 0.0324 and a median survival for cefepime of 22 days vs. 16 for the comparator.

Figure 25: Kaplan-Meier survival curve for timing of death with death occurring within 30 days of end of treatment in the cefepime and comparator arms
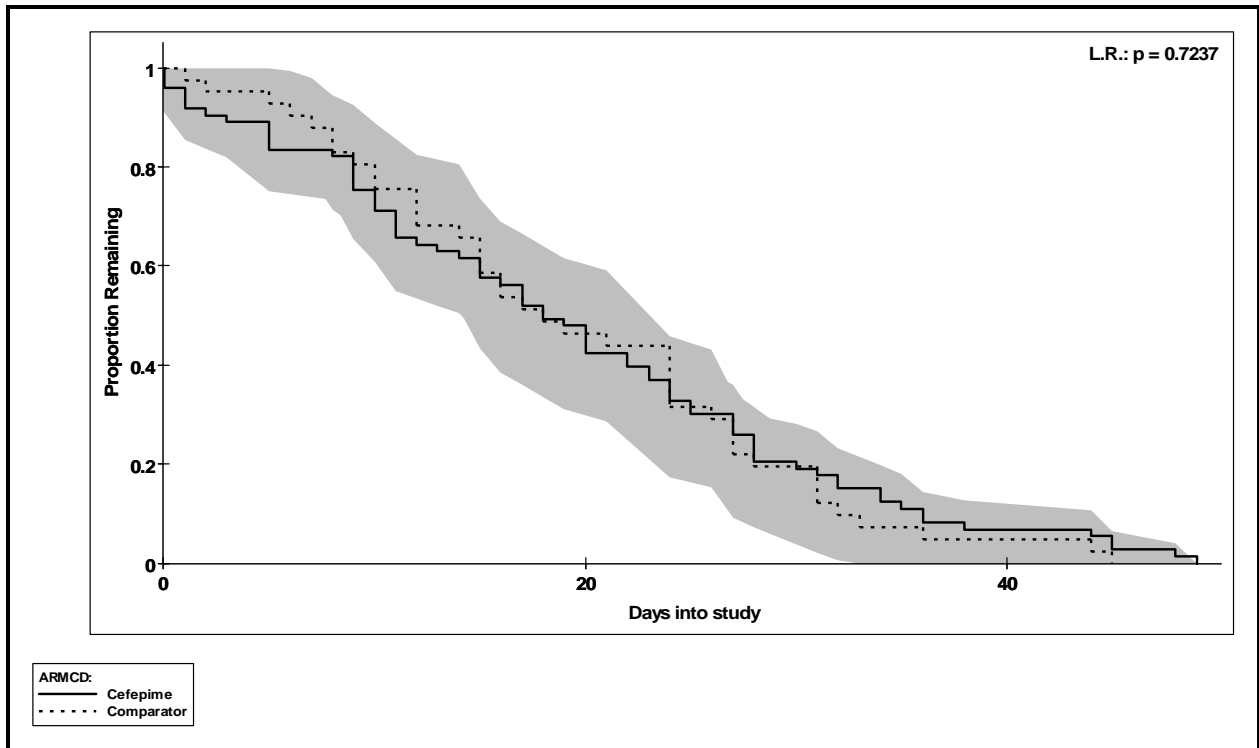
Figure 26: Kaplan-Meier survival curves for death, by study
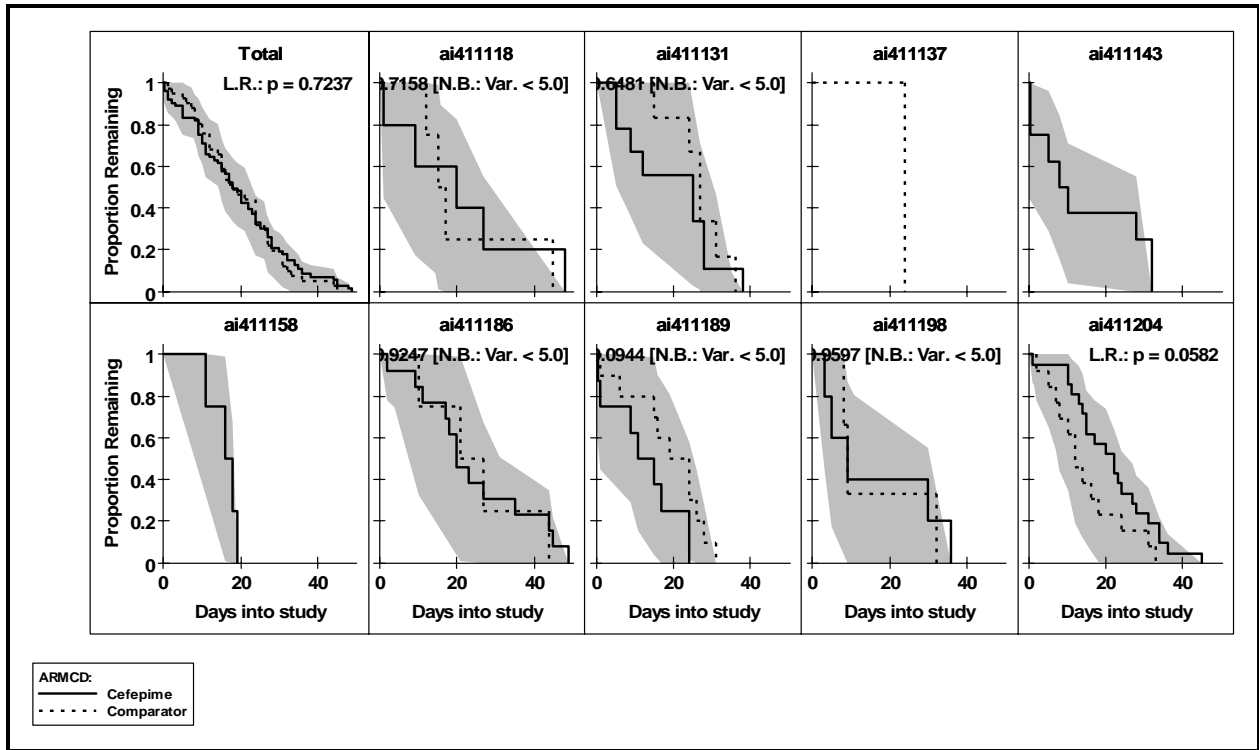
Figure 27: Kaplan-Meier survival curves for death, by sex
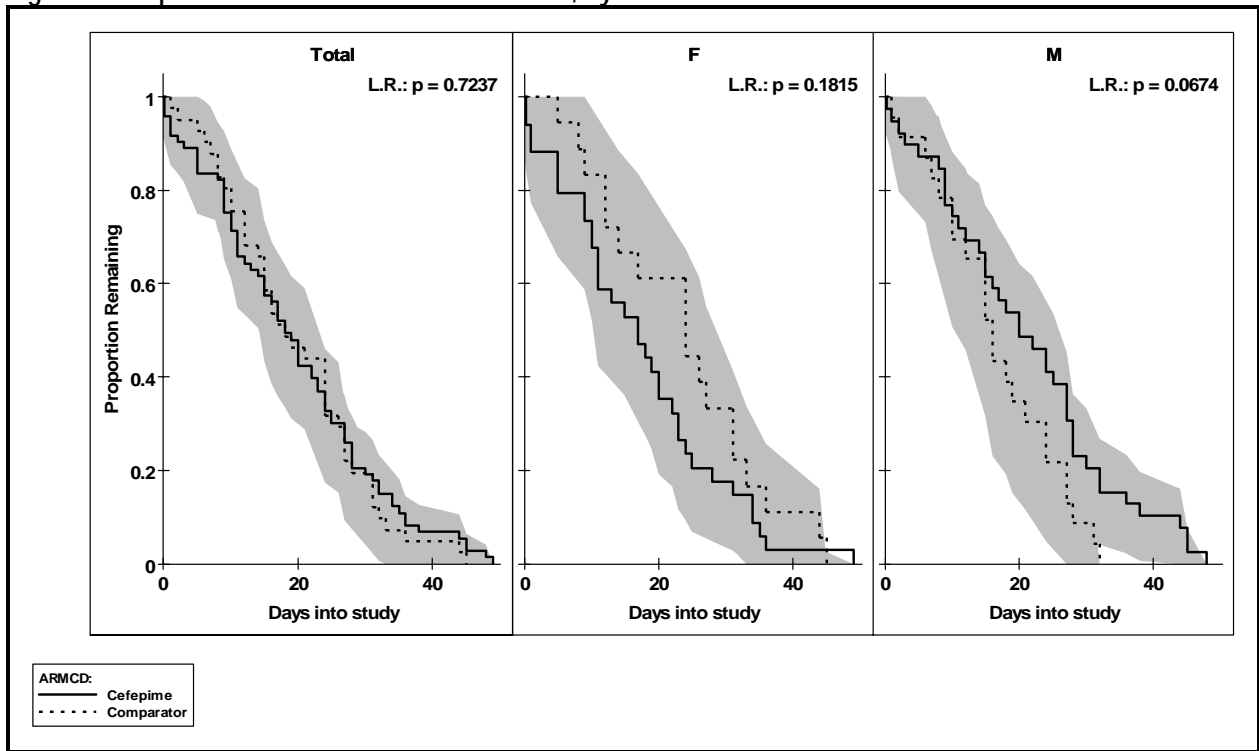
Figure 28: Kaplan-Meier survival curves for death, by race
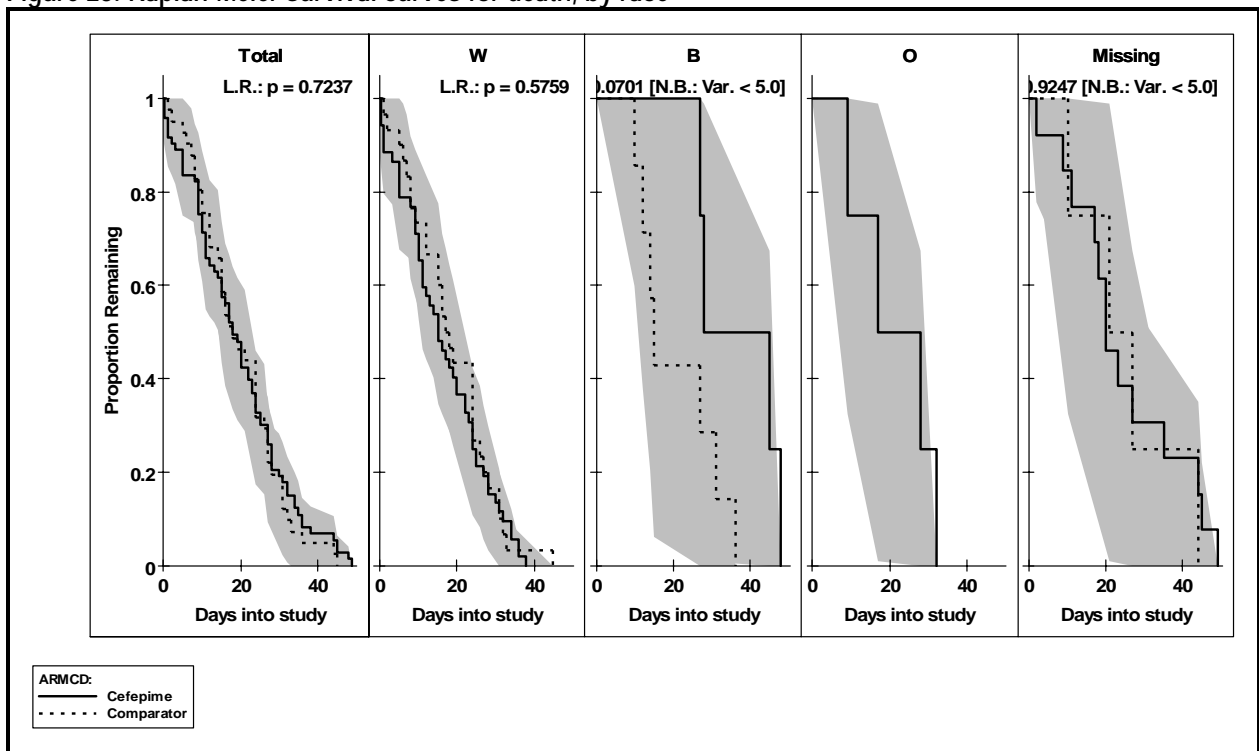
Figure 29: Kaplan-Meier survival curves for death, by age
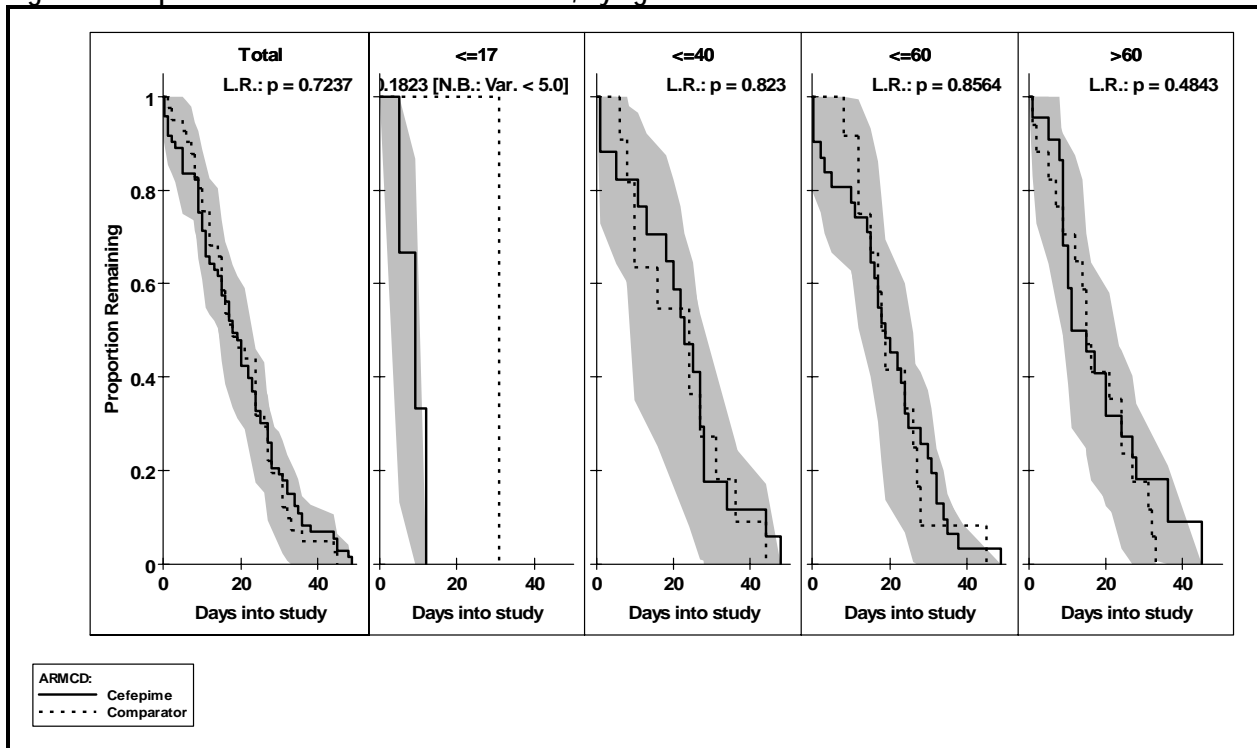
Figure 30: Kaplan-Meier survival curves for death for patients with and without AL, AMM, BMT, and ST
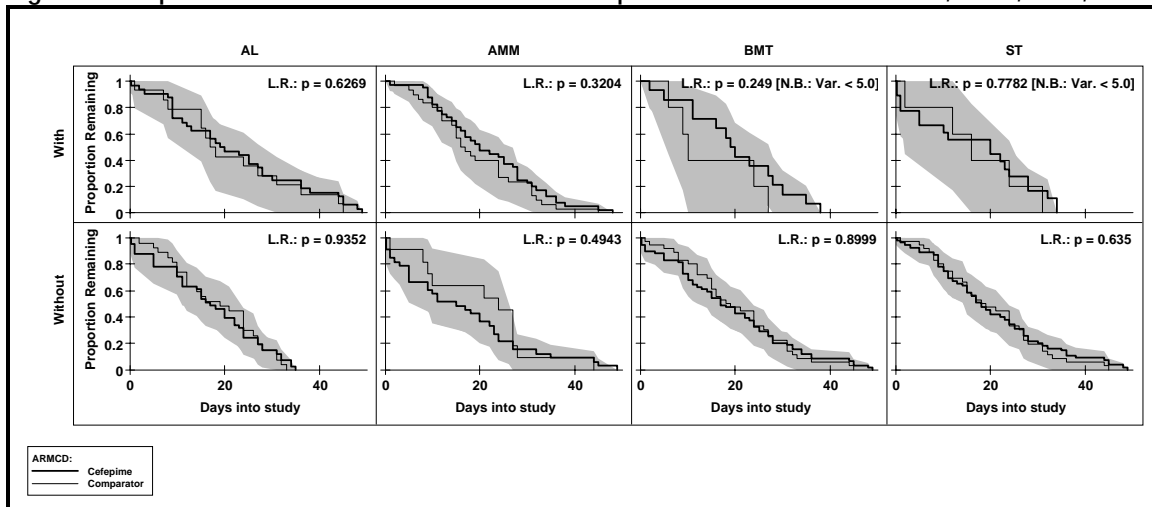
4.12.2.   *"Napoleon's March" Displays*

Around 1995, the CARS (Computer Assisted Review of Safety) Committee worked with Belmont Research to design a graphic display that Jonathan Levine nicknamed the "Napoleon's March." This graphic display portrays in a common time line the timing of selected events (in this case death), and EOT for each patient in a clinical trial (17). Every patient occupies a different row in the display, and the patients are ranked by a variable (in this case the timing of death). The original "Napoleon's March" graphic display that was designed by Charles Joseph Minard, portrays the losses suffered by Napoleon's army in the Russian campaign of 1812 (18).

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In this review, we use the "Napoleon's March" graphic analysis to highlight several interesting patterns for the subset of patients who died.

We show that we studied what we planned to do, since the days to death following end of exposure (black squares) were 30 days or less (Figure 31).

Cefepime deaths tended to occur more in the beginning of treatment or later in the end of the observation period than the comparator (Figure 32).

Although not statistically significant, death occurred in Study ai411204 (the study with the highest proportion of cefepime deaths), on day 45 or earlier and on day 33 or earlier in the cefepime and comparator patients, respectively (Figure 33).

In males, death occurred sooner in the comparator patients, with a similar proportion of deaths in both treatment arms (Figure 34). In females, the days to death show a similar pattern in both treatment arms (Figure 35).

We also used the "Napoleon's March" graphic analysis to study the relationship between the timing of severe neutropenia (defined by a neutrophil count of >=100 U/µL), death (19), and end of treatment (EOT). Figure 36 helped us understand that we could not study the timing of severe neutropenia and death because the sponsor stopped collecting neutrophil counts after EOT.

Figure 31: "Napoleon's March" display of days to death following EOT ( ). Patients sorted by death day following EOT. The y-axis shows patients unique identifiers

Days to death following EOT

Cefepime (73 deaths [8.2% of 890 enrolled])

Comparator (41 deaths [7.5% of 626 enrolled])
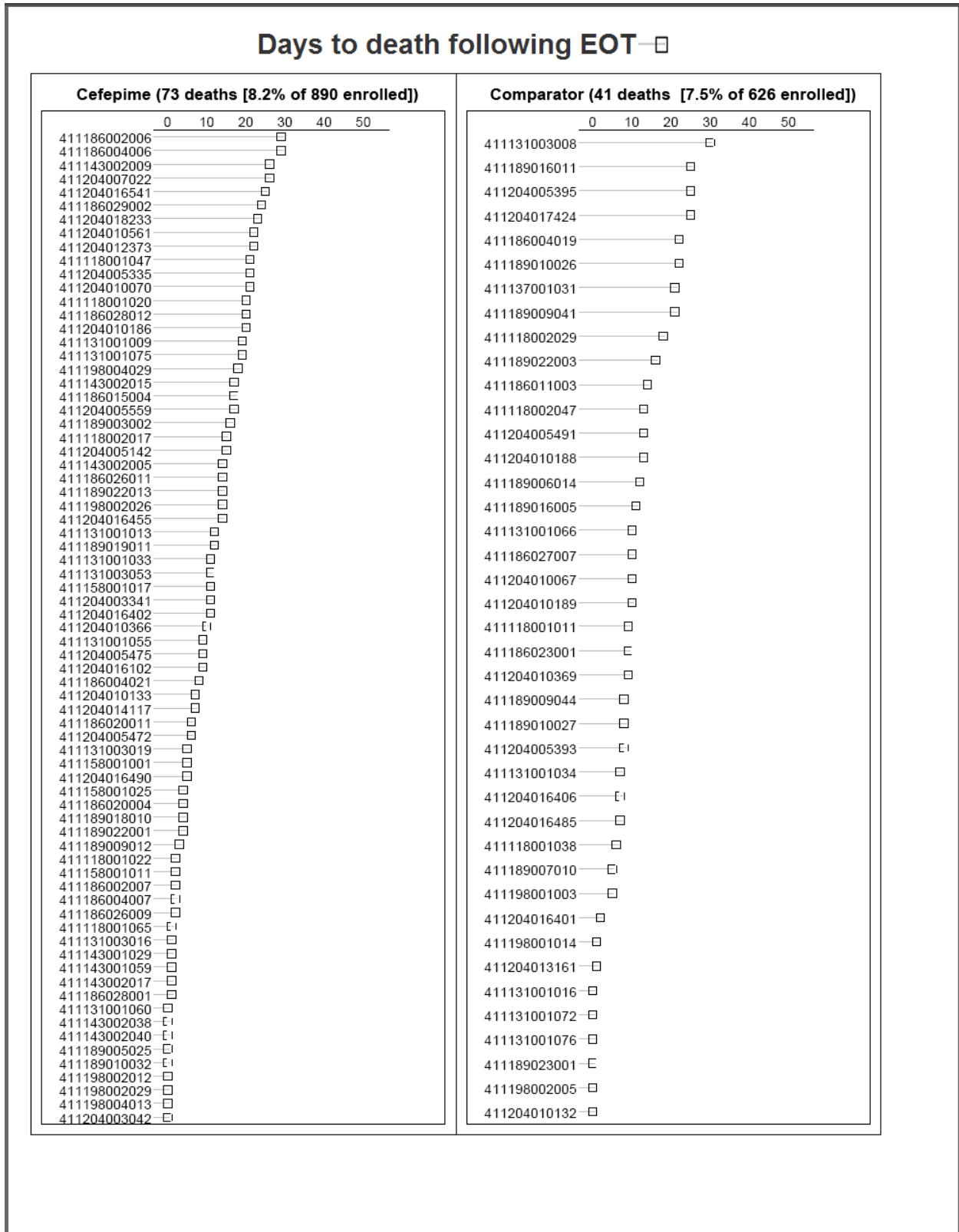
Figure 32: "Napoleon's March" display, but showing days to EOT (O) and days to death ( ) following randomization. Patients sorted by day of death
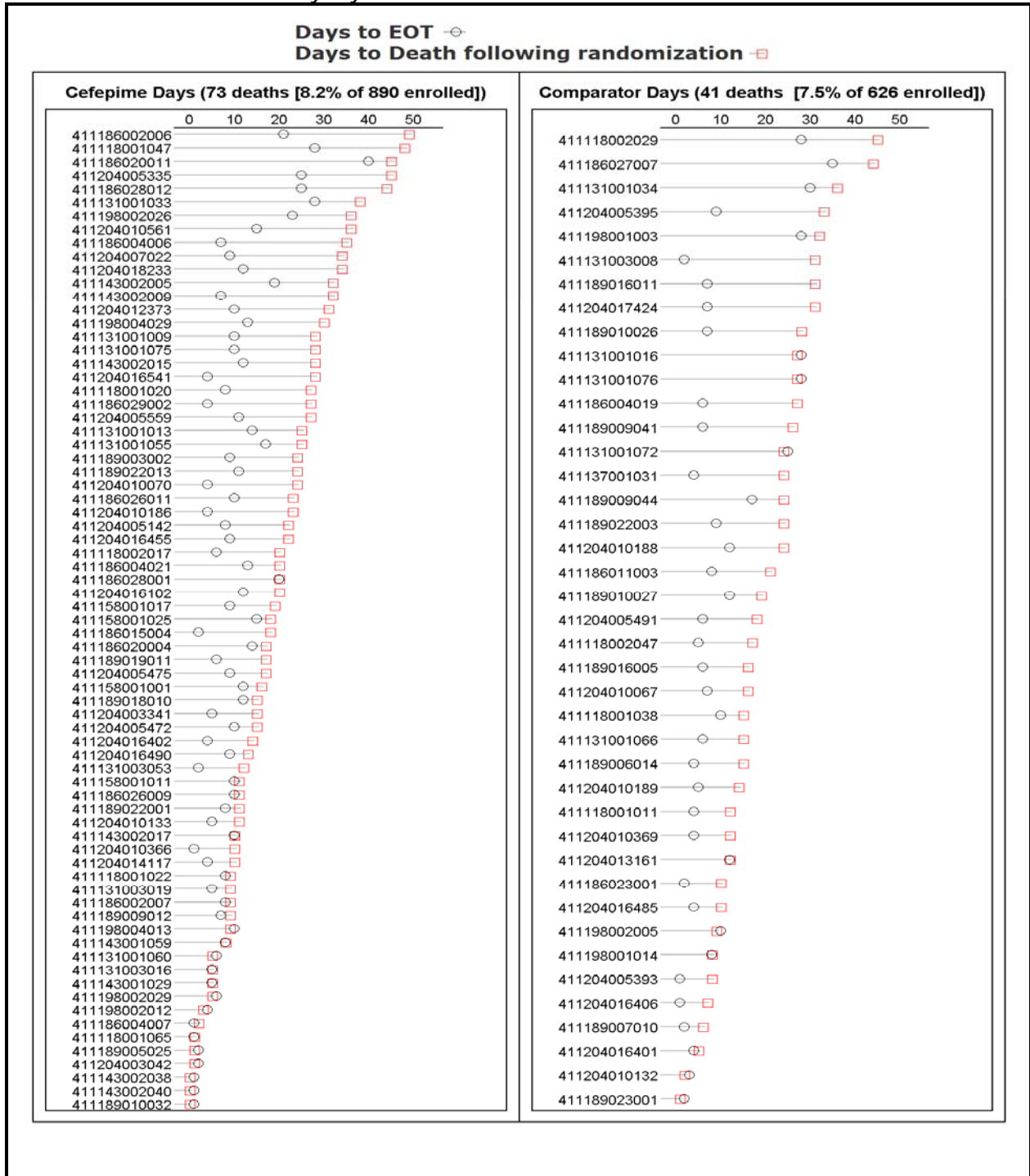
Figure 33: "Napoleon's March" display as the previous one, but for study ai411204
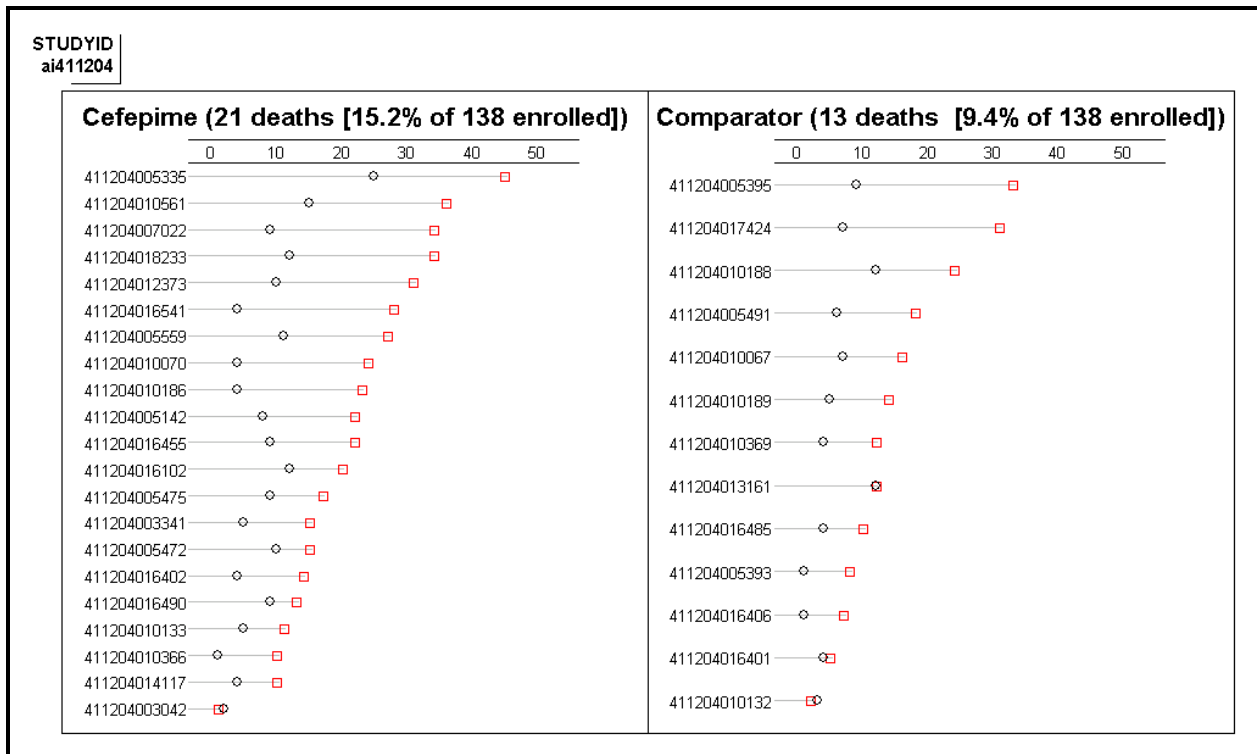
Figure 34: "Napoleon's March" display as the previous one, for males
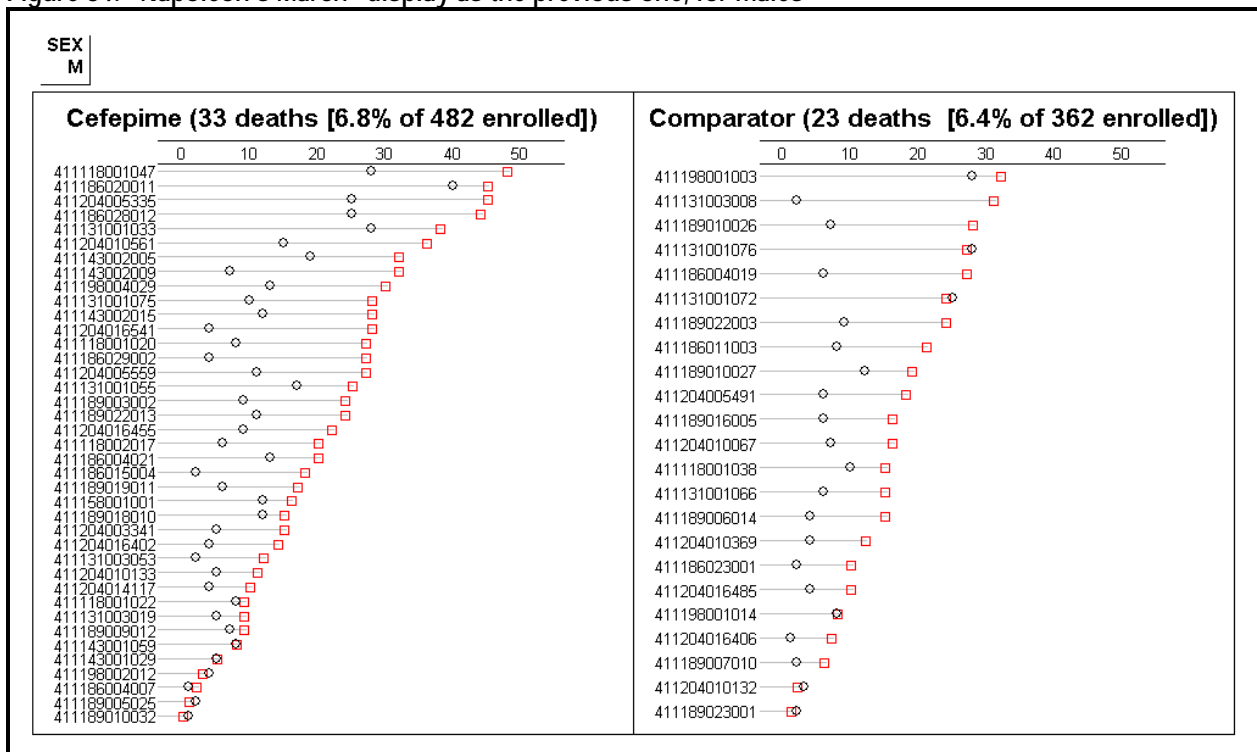
Figure 35: "Napoleon's March" display as the previous one, but for females
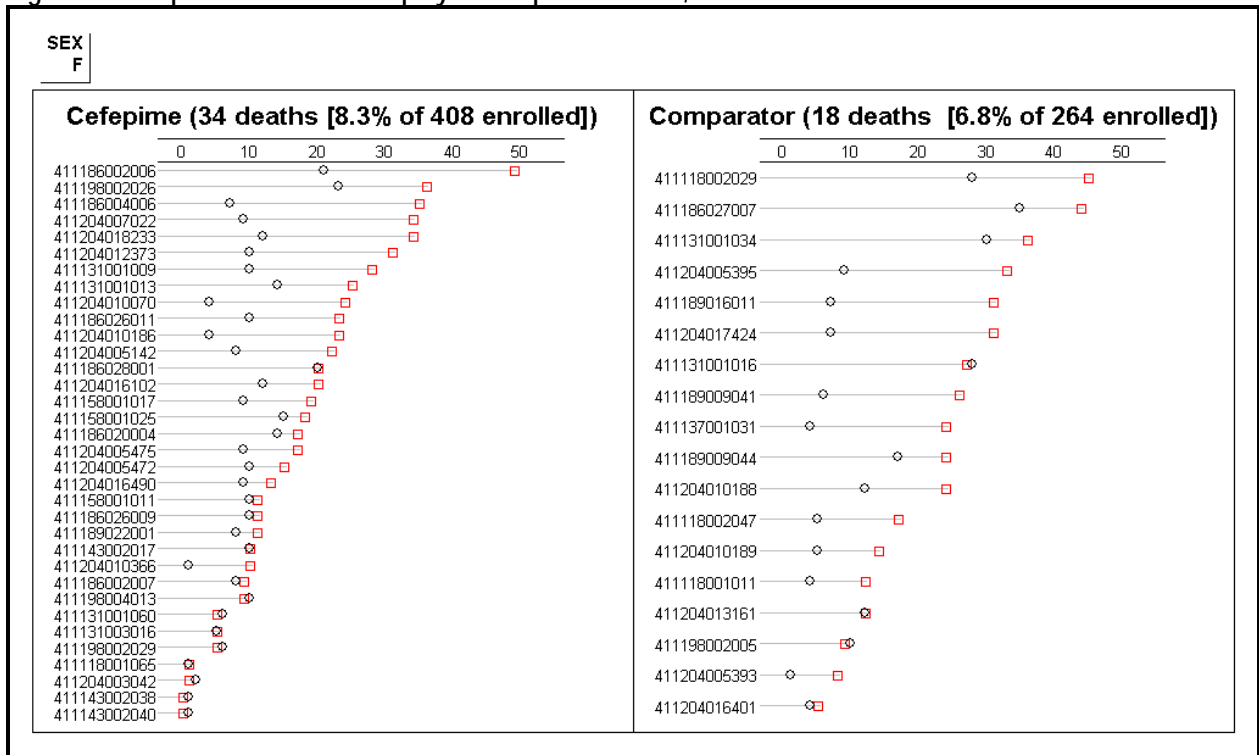
Figure 36: "Napoleon's March" display of timing of neutrophil count values
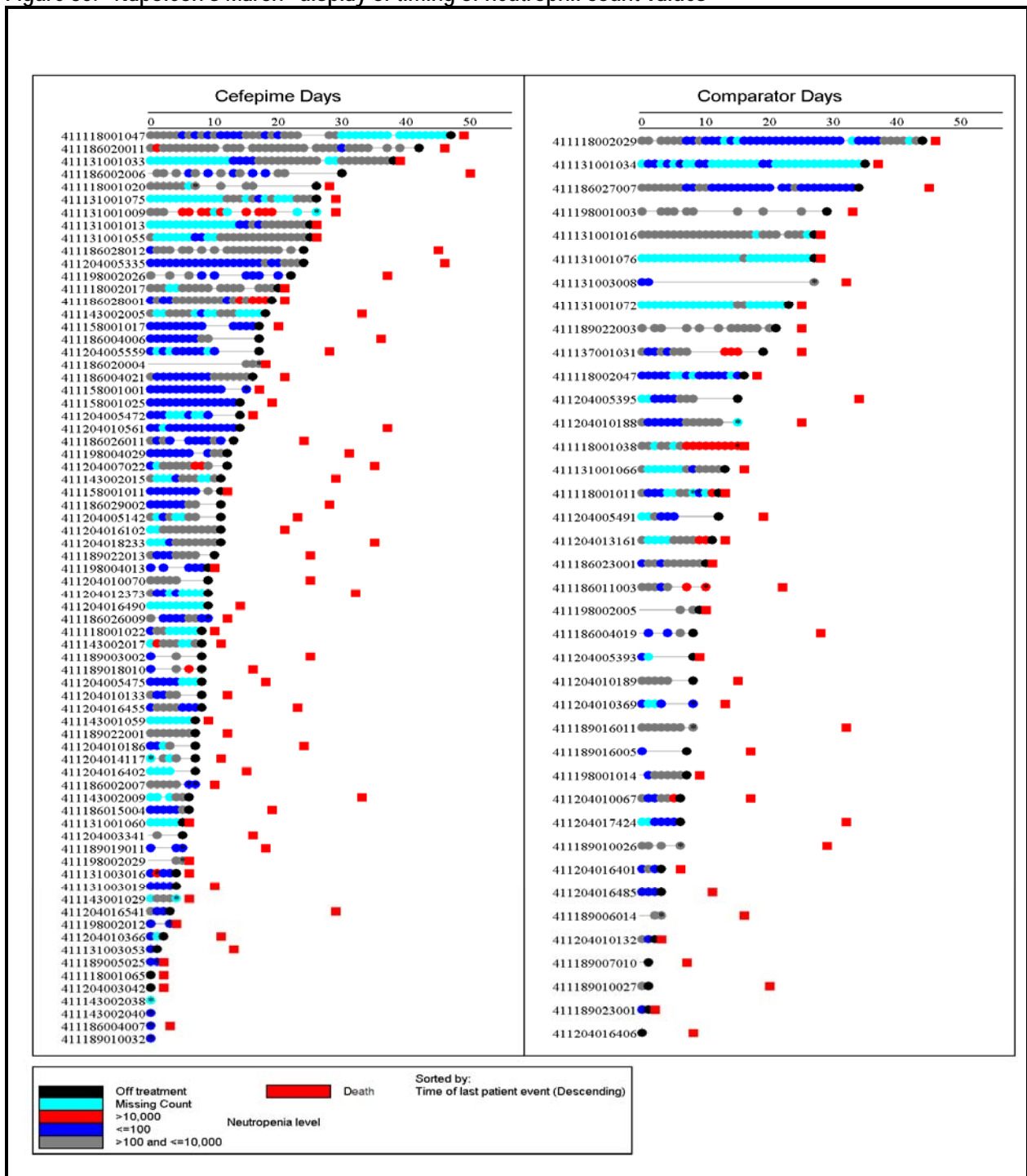
Blue: <=100, gray: >100 and <=10,000, red: >10,000 and cyan: missing count] by day of enrollment, showing EOT (●) and death (■) [* shows data collision]

4.13. *Potential Syndromes*

The cluster selection focuses at identifying which responses act similarly; not which ones are the most significant associations.

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We run Cluster Mining with the Following Configuration Options: Clustering Method=Complete; Minimum SOR=1.5; Minimum # Issues=3; Issues Shared Across Issue Clusters=true

We identified several issue clusters that contained death as an event.

We selected to describe Cluster #34 in more detail to document what the software was generating

The issue Cluster #34 had a Syndrome OR (SOR)=1.63. It included the following events:

1) PT: Oral mucosal erythema,

2) PT: Mouth haemorrhage,

3) PT: Death,

4) SMQ: CNS haemorrhages and cerebrovascular accidents [narrow],

5) SMQ: Haemorrhagic cerebrovascular conditions [narrow]

The next screen shots illustrate the process of assessing an Issue Cluster:

Figure 37: Cluster miner—display of 5 events in Cluster #34
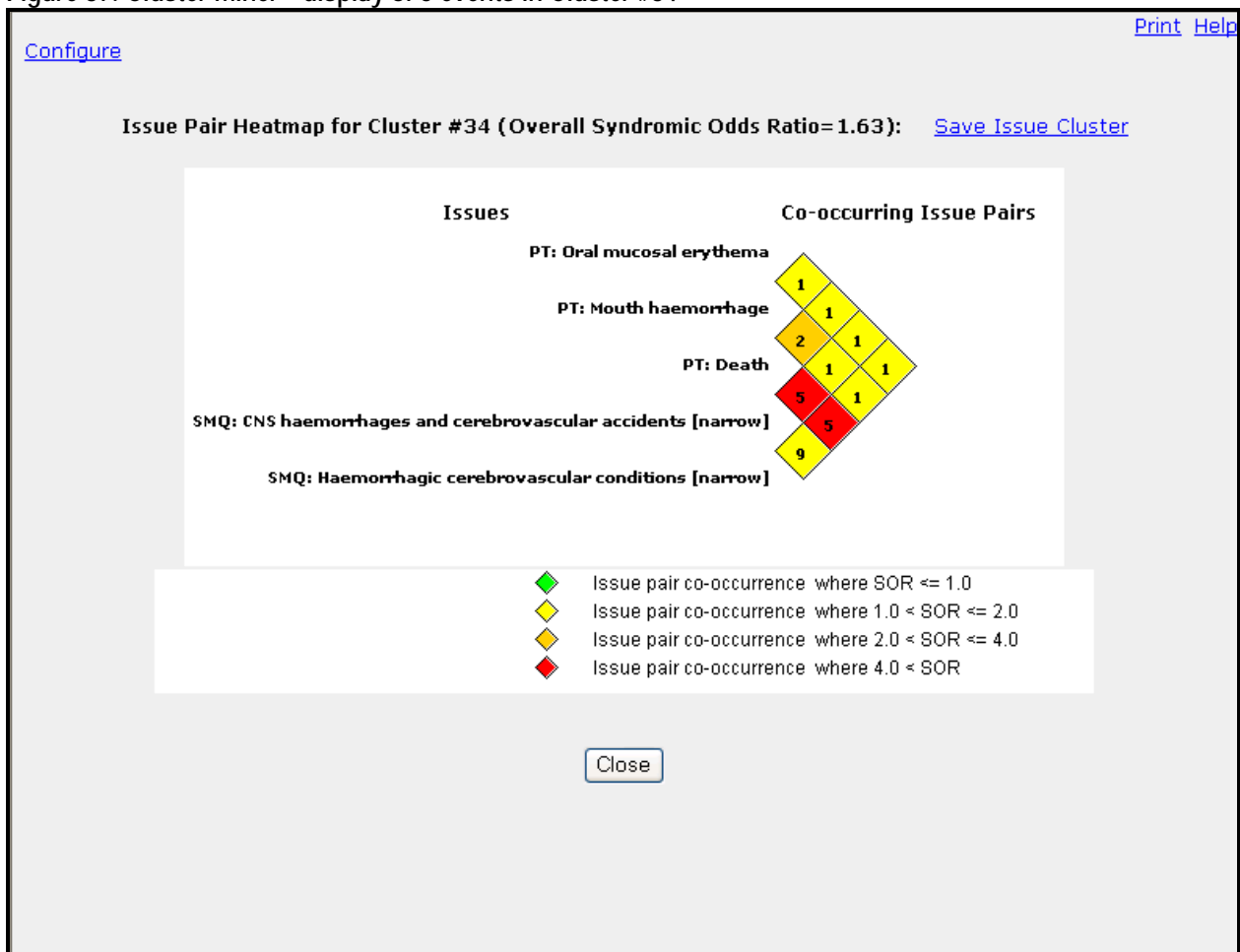
Figure 38: Highlight of event pairs in the same cluster—PT: Death and SMQ: CNS haemorrhages and cerebrovascular accidents [narrow]
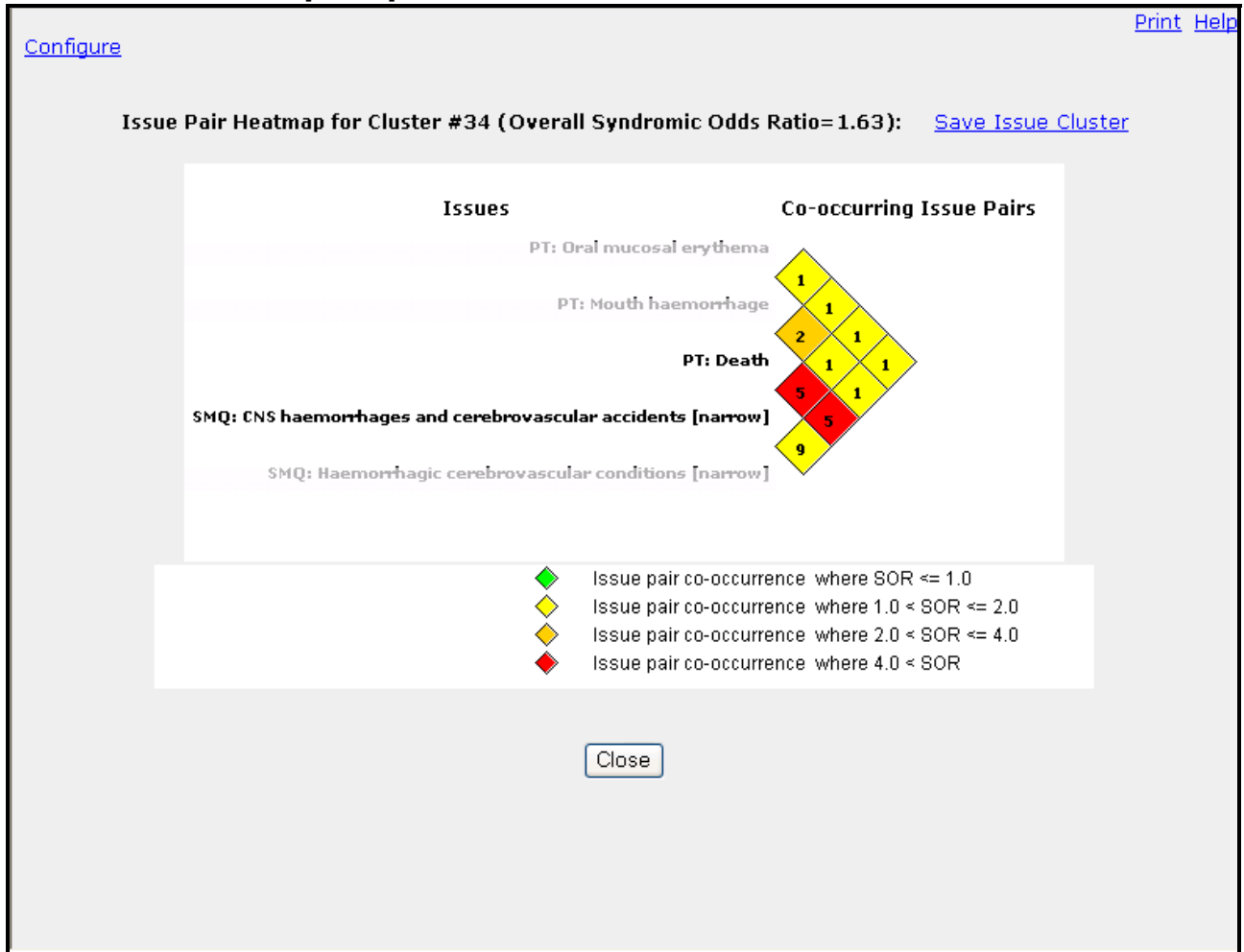
Figure 39: Highlight of event pairs in the same cluster —PT: Death and SMQ: Haemorrhagic cerebrovascular conditions [narrow]
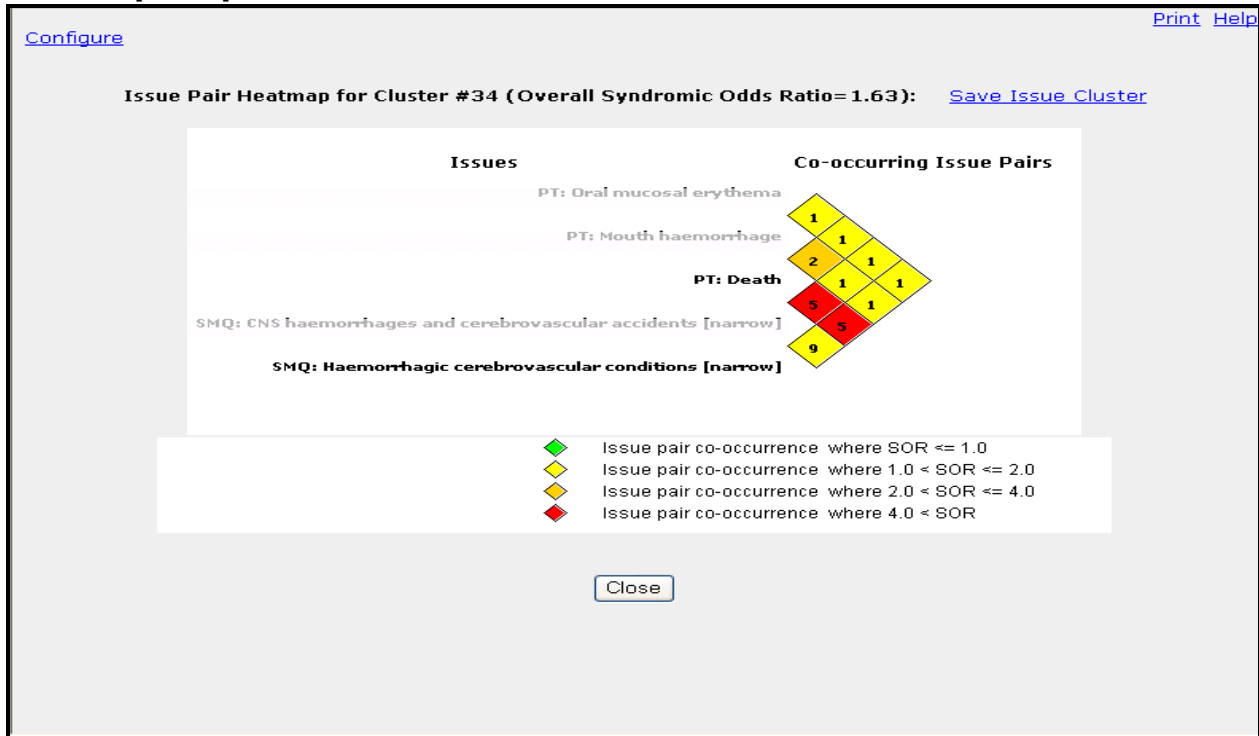
Figure 40: Highlighting event pairs in the cluster—PT: Mouth haemorrhage and PT: Death

Figure 41: Observed and estimated population percentages for SMQ: Haemorrhagic cerebrovascular conditions [narrow] + PT: Death

Help

Statistics associated with the Issue pair 'Haemorrhagic cerebrovascular conditions [narrow]' + 'Death' (Observed in 5 Subjects):

Observed and Estimated Population Percentages:

	Treatment	Comparator
Observed	0.562%	0.000%
Empirical Bayes Estimate Under independence	0.05%	0.037%
Empirical Bayes Estimate with Secondary Shrinkage	0.176%	0.03%

Empirical Bayes Odds Ratio (confidence interval): 5.95 (0.1, 338.25)

Syndromic Odds Ratio: 4.36

Close

Figure 42: Observed and estimated population percentages for SMQ: CNS haemorrhages and cerebrovascular accidents [narrow] + Death

Help

Statistics associated with the Issue pair 'CNS haemorrhages and cerebrovascular accidents [narrow]' + 'Death' (Observed in 5 Subjects):

Observed and Estimated Population Percentages:

	Treatment	Comparator
Observed	0.562%	0.000%
Empirical Bayes Estimate Under independence	0.055%	0.042%
Empirical Bayes Estimate with Secondary Shrinkage	0.187%	0.033%

Empirical Bayes Odds Ratio (confidence interval): 5.69 (0.12, 263.99)

Syndromic Odds Ratio: 4.4

Close

Figure 43: Observed and estimated population percentages for PT: Mouth haemorrhage + Death

Help

Statistics associated with the Issue pair 'Mouth haemorrhage' + 'Death' (Observed in 2 Subjects):

Observed and Estimated Population Percentages:

	Treatment	Comparator
Observed	0.225%	0.000%
Empirical Bayes Estimate Under independence	0.022%	0.016%
Empirical Bayes Estimate with Secondary Shrinkage	0.048%	0.015%

Empirical Bayes Odds Ratio (confidence interval): 3.27 (0.01, 1284.18)

Syndromic Odds Ratio: 2.37

Close

Figure 44: Confidence interval graph for the same cluster
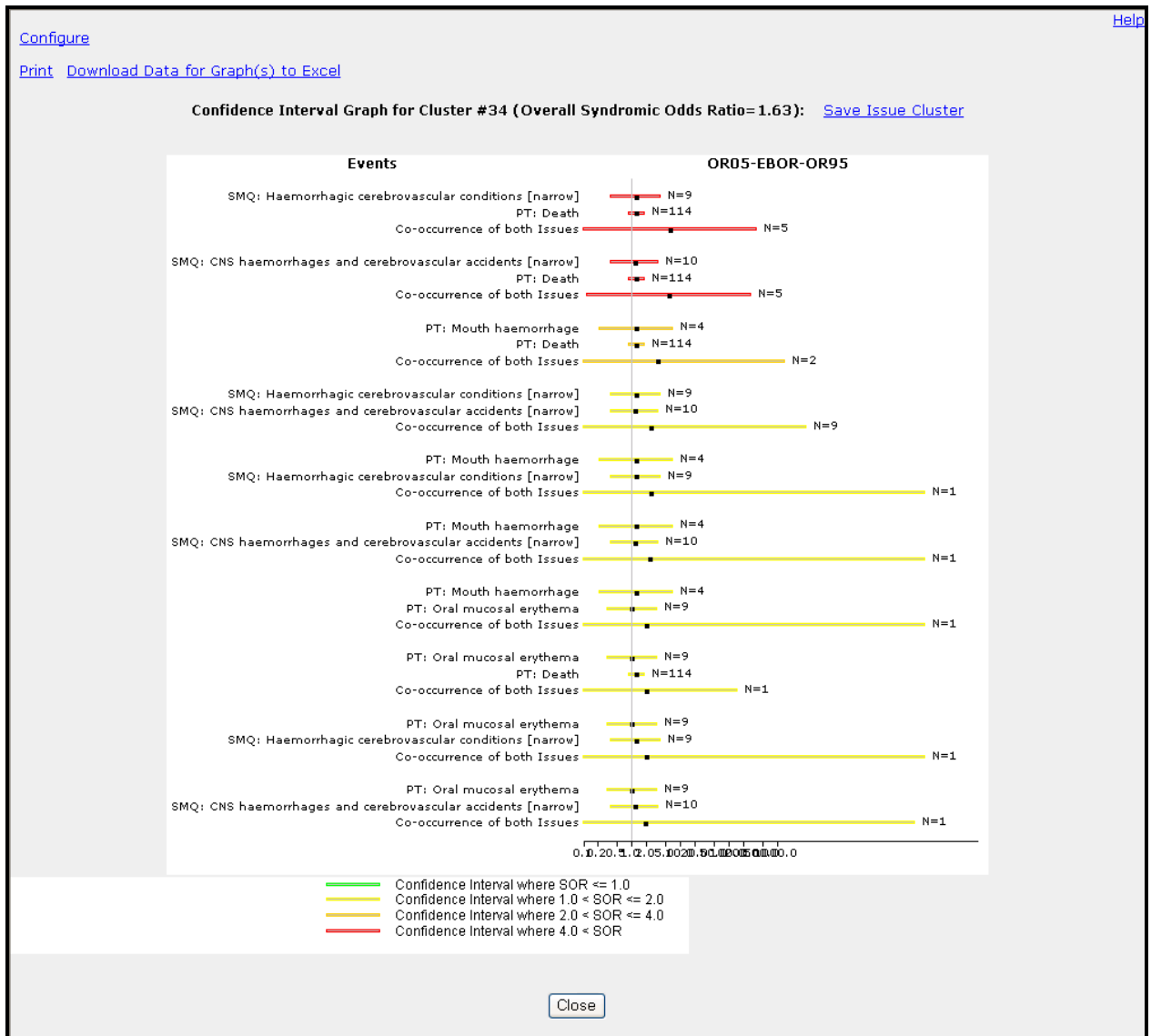
Figure 45: Statistics for the same issue cluster

Statistics related to Issue Cluster "Clustter # 34":

Counts and Percents of Subjects Experiencing Issues:

| | | Subjects | | | | | |
| | | Overall | | Treatment Group* | | Comparator Group* | |
Issue Type	Issue Name	N	%	N	%	N	%
PT	Oral mucosal erythema	9	0.59	5	0.56	4	0.64
PT	Mouth haemorrhage	4	0.26	4	0.45	0	0
PT	Death	114	7.52	73	8.2	41	6.55
SMQ	CNS haemorrhages and cerebrovascular accidents [narrow]	10	0.66	7	0.79	3	0.48
SMQ	Haemorrhagic cerebrovascular conditions [narrow]	9	0.59	7	0.79	2	0.32

* Treatment and Comparator data are based on the dosing breakdown 'Arm of last randomization' defined for study 'All 9 studies FN LE'

Actual and Expected Counts of Subjects Experiencing Exactly N of the Issues:

| | Subjects | | | | | |
| | Overall | | Treatment Group* | | Comparator Group* | |
N	Actual #	Expected #	Actual #	Expected #	Actual #	Expected #
0	1387	1372.6	809	796.1	578	576.6
1	119	140.8	73	91.8	46	48.7
2	5	2.6	3	2.0	2	0.6
3	4	0.0	4	0.0	0	0.0
4	0	0.0	0	0.0	0	0.0
5	1	0.0	1	0.0	0	0.0

* Treatment and Comparator data are based on the dosing breakdown 'Arm of last randomization' defined for study 'All 9 studies FN LE'

Close

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4.14. *Adjusted EBOR Values Across 25 MBLR Runs*

Figure 46: Overall EBOR values by runs, covariates, and issues analyzed

Figure 47: EBOR values for "Sex:F" by runs, covariates, and issues analyzed

Issues Selected:
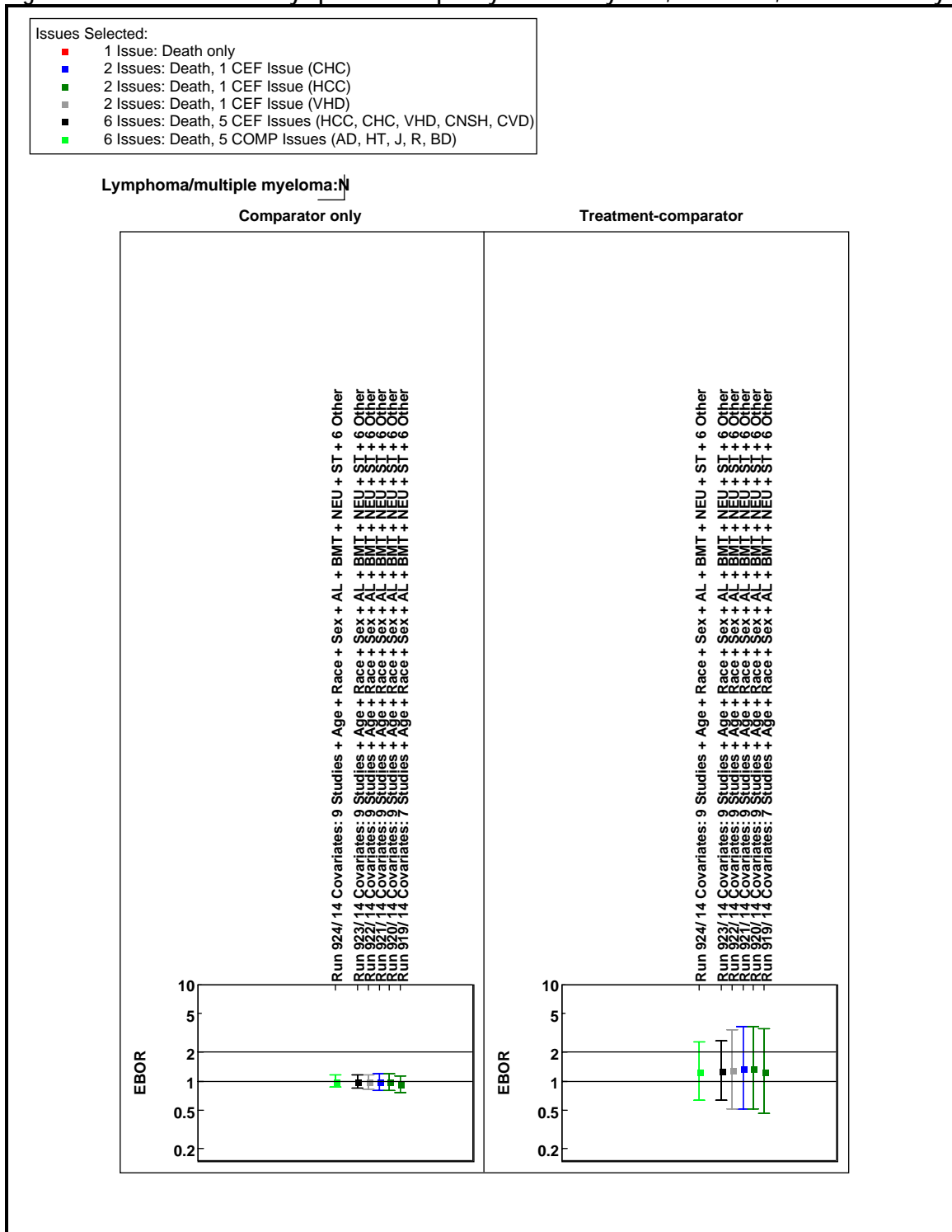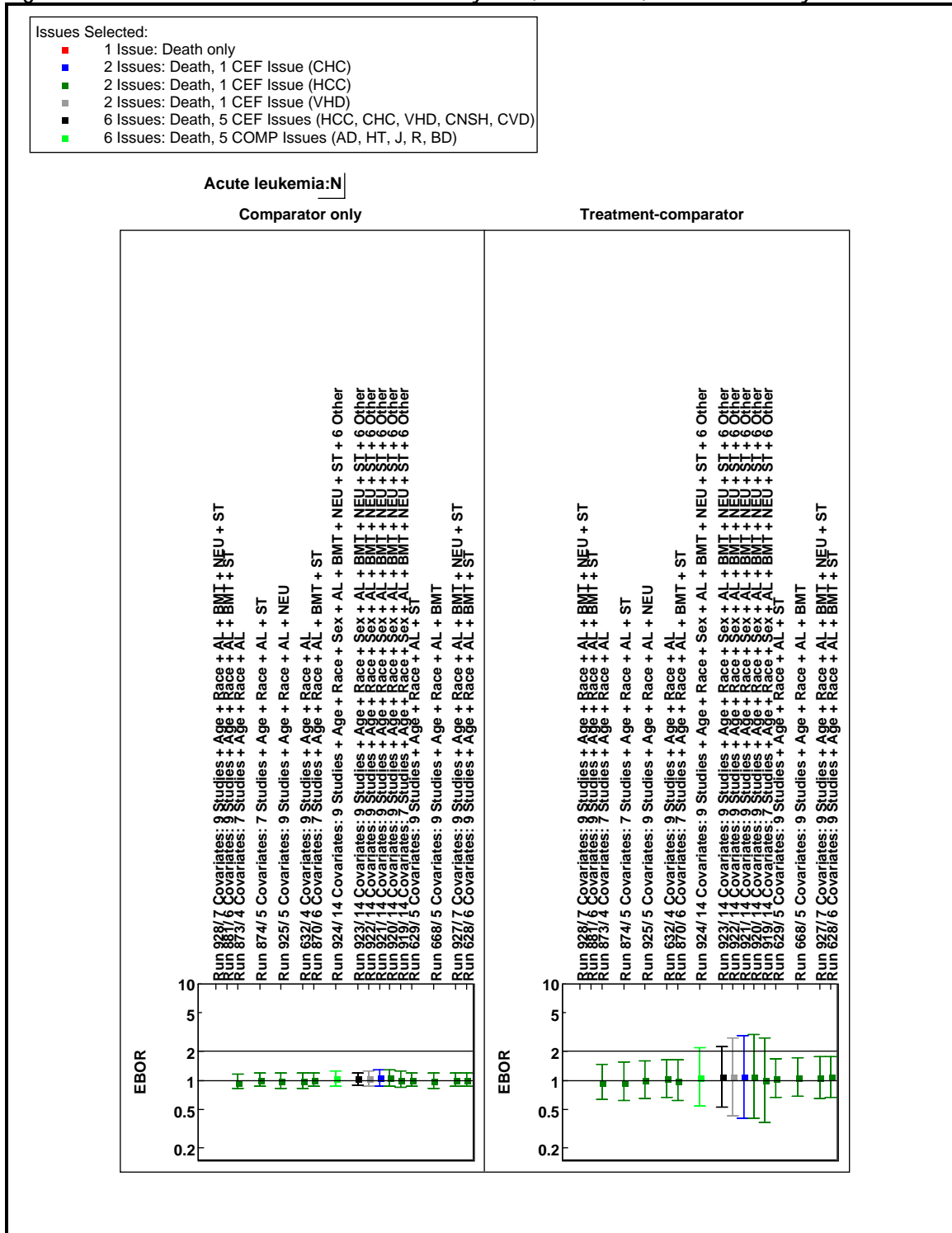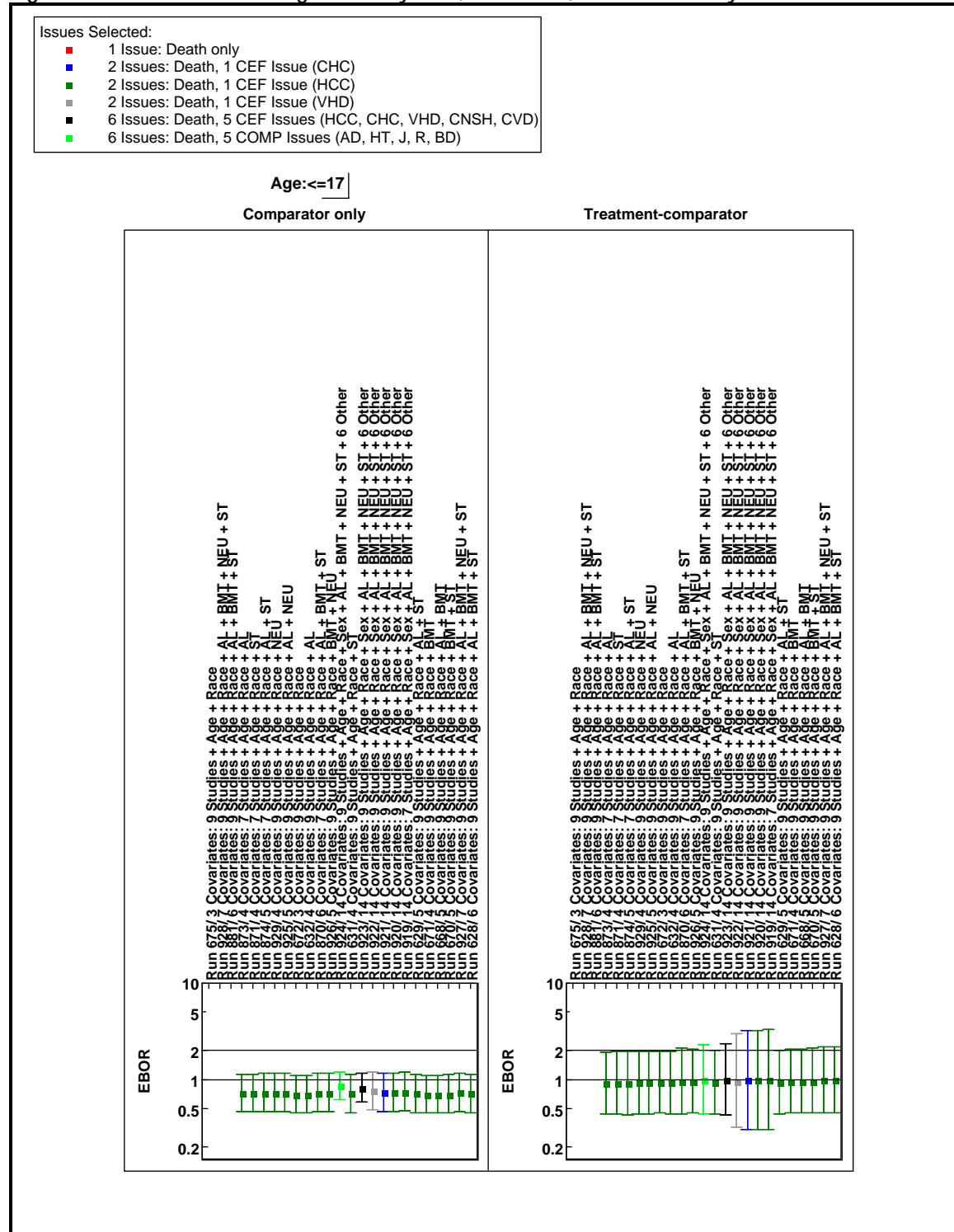- 1 Issue: Death only
- 2 Issues: Death, 1 CEF Issue (CHC)
- 2 Issues: Death, 1 CEF Issue (HCC)
- 2 Issues: Death, 1 CEF Issue (VHD)
- 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Sex:F

Comparator only

Treatment-comparator
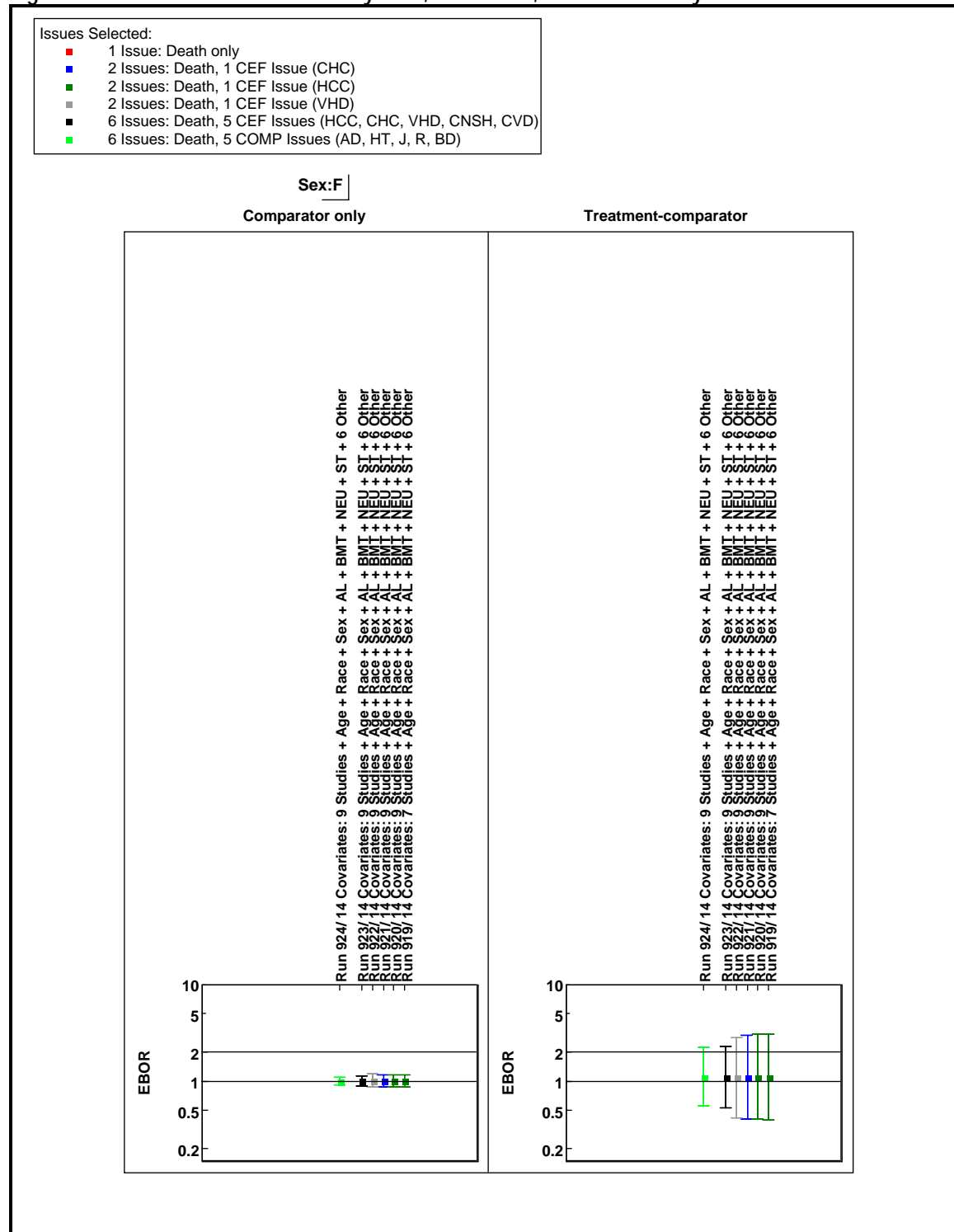
Figure 48: EBOR values for "Sex:M" by runs, covariates, and issues analyzed
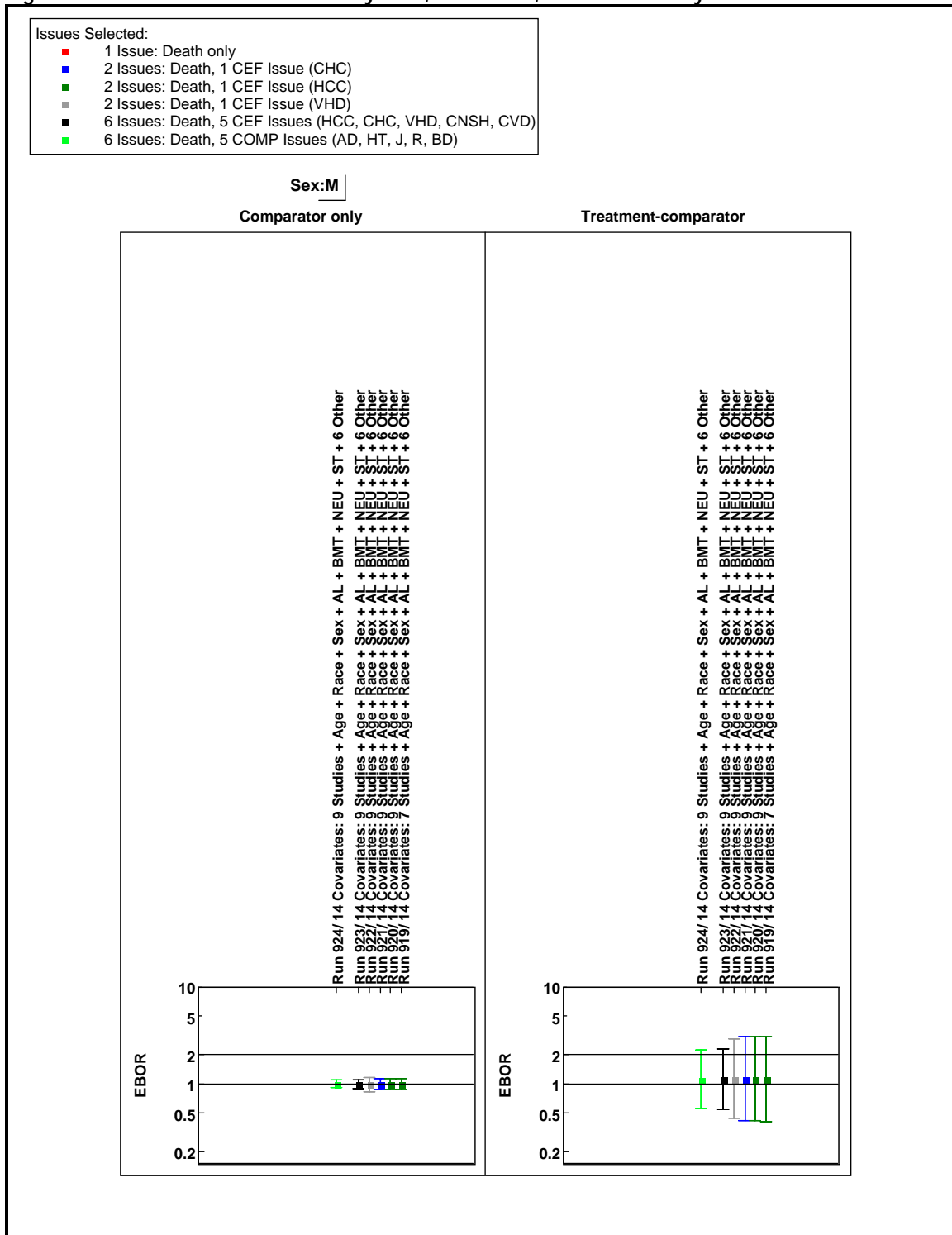
Figure 49: EBOR values for "Race:Other" by runs, covariates, and issues analyzed
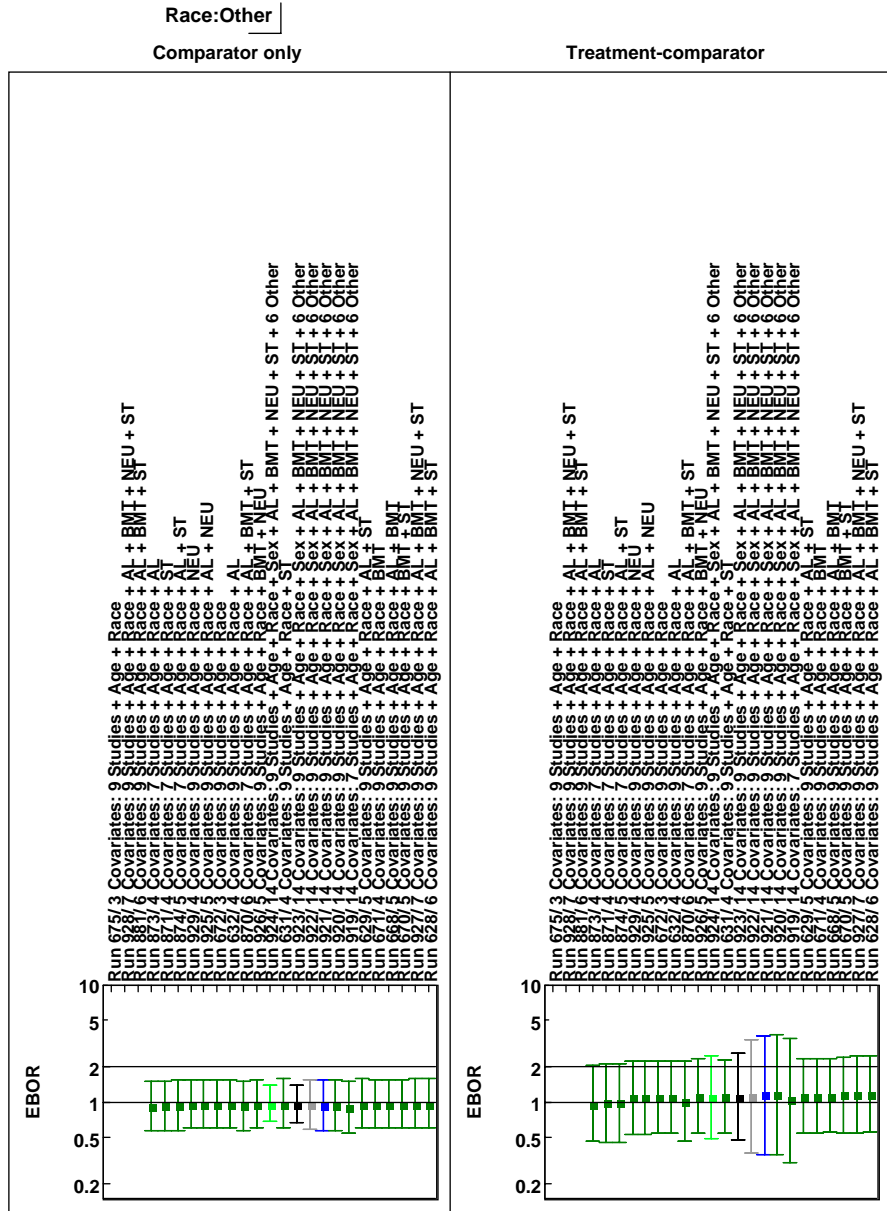
Figure 50: EBOR values for "Race:Black" by runs, covariates, and issues analyzed
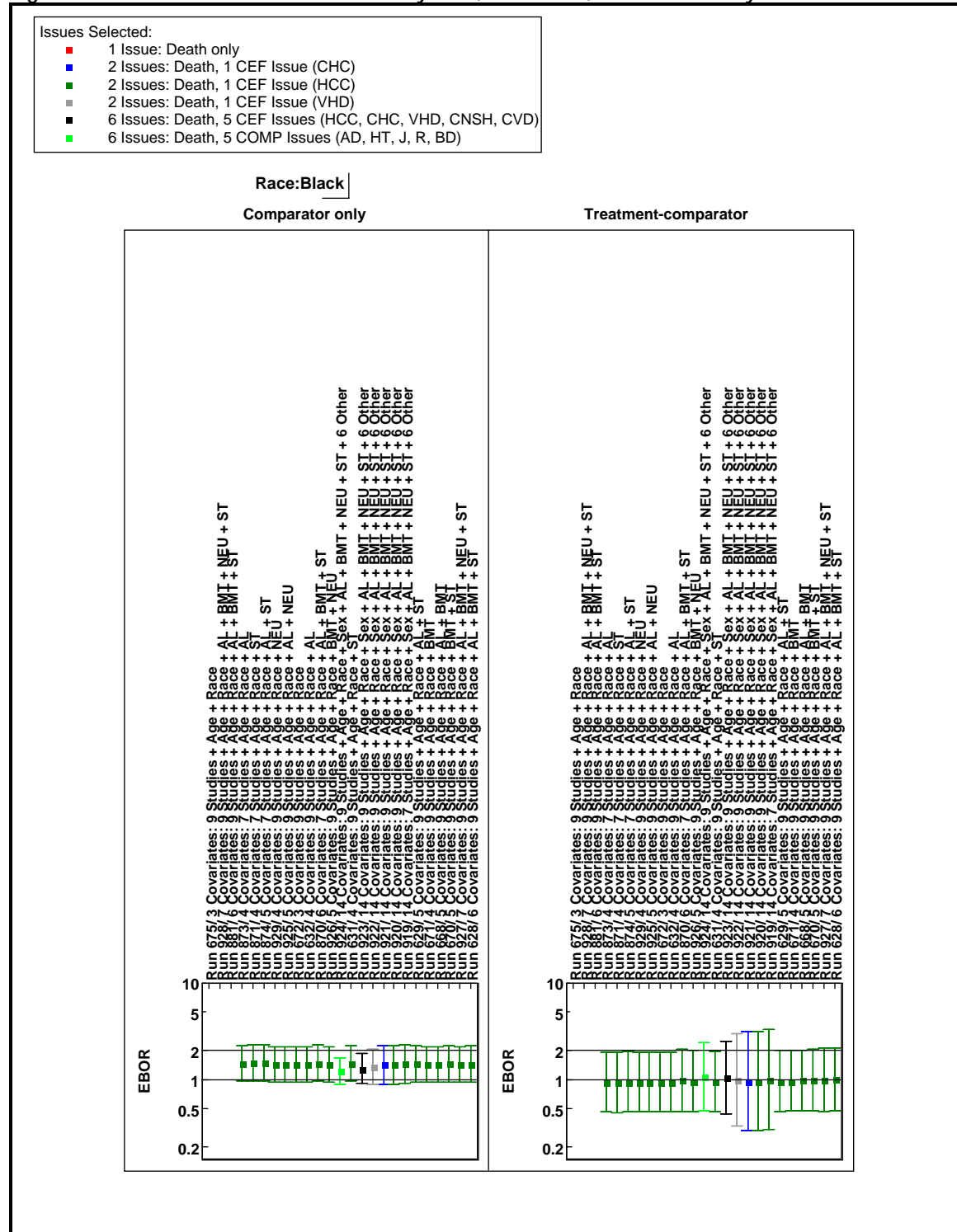
Figure 51: EBOR values for "Race:White" by runs, covariates, and issues analyzed
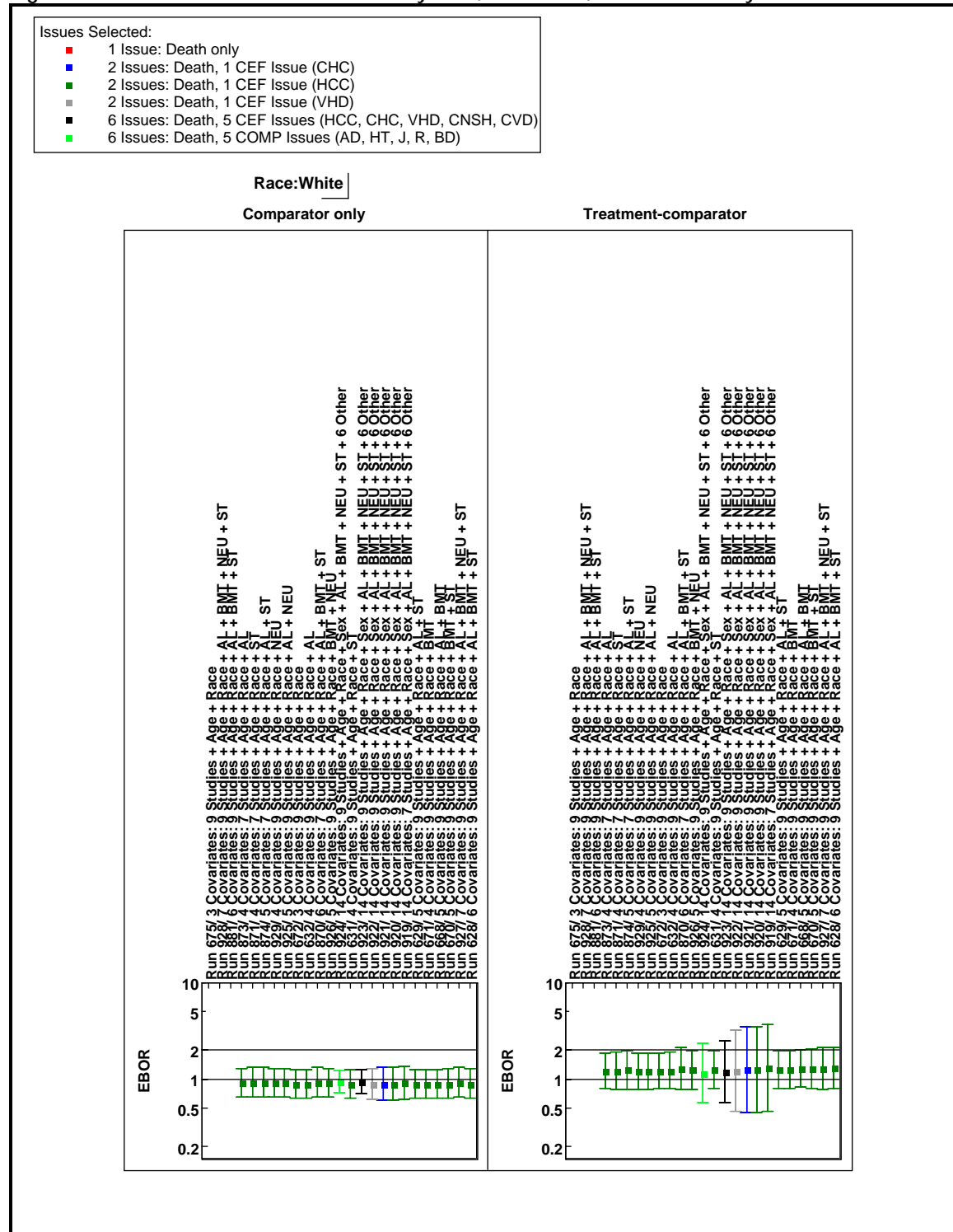
Figure 52: EBOR values for "Race:Other or Not Specified" by runs, covariates, and issues analyzed
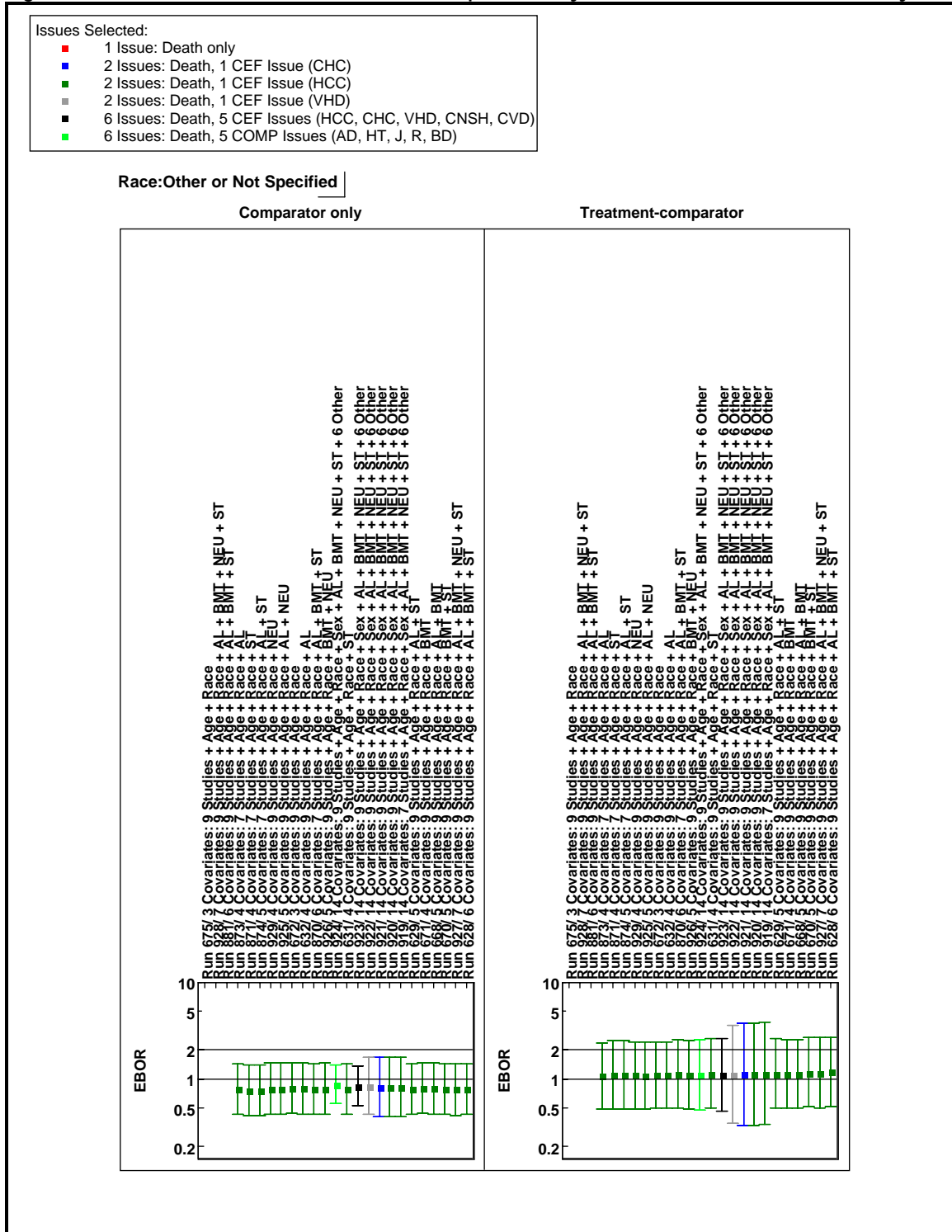
Figure 53: EBOR values for "CS ai411118" by runs, covariates, and issues analyzed
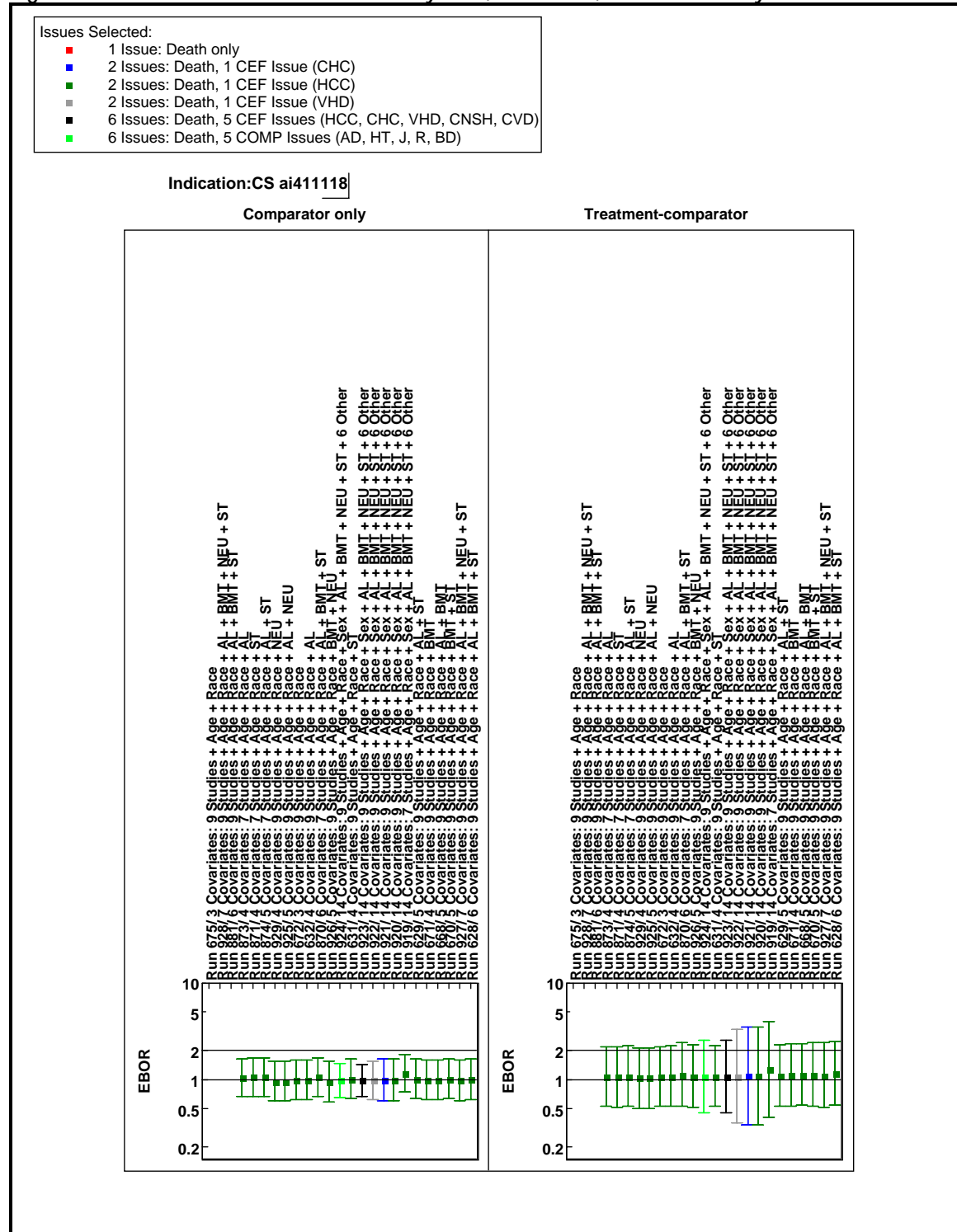
Figure 54: EBOR values for "CS ai411131" by runs, covariates, and issues analyzed
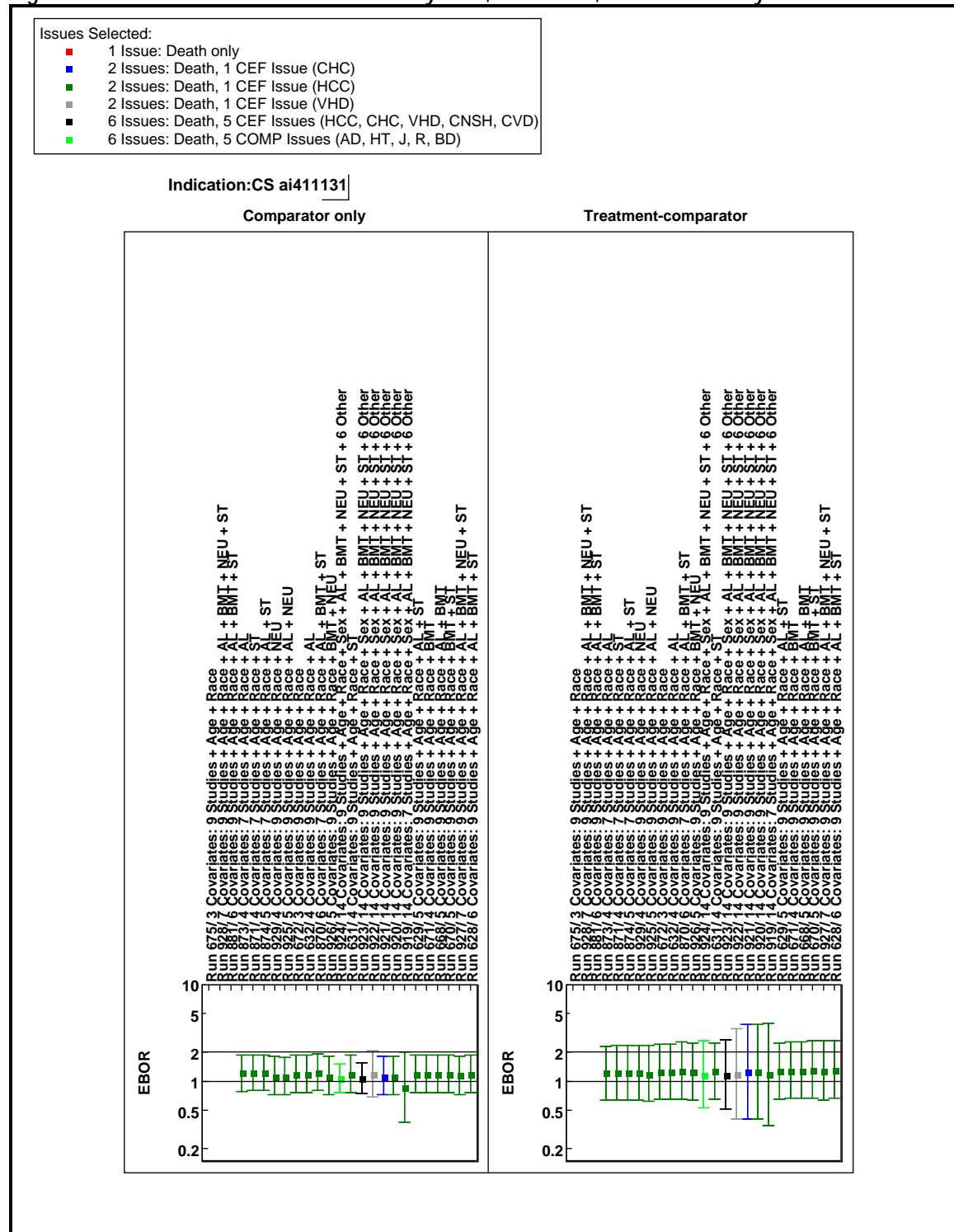
Figure 55: EBOR values for "CS ai411186" by runs, covariates, and issues analyzed
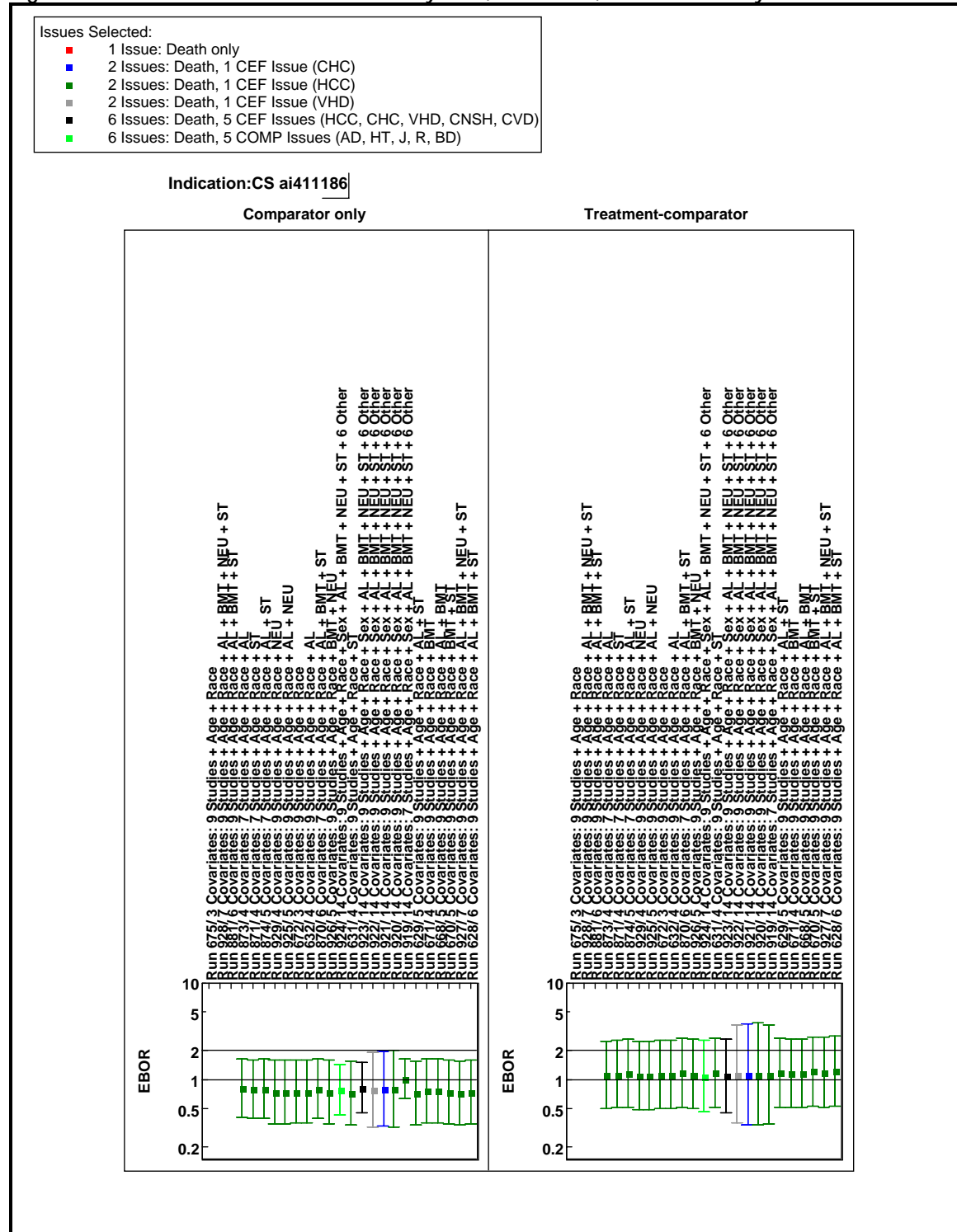
Figure 56: EBOR values for "CS ai411137" by runs, covariates, and issues analyzed
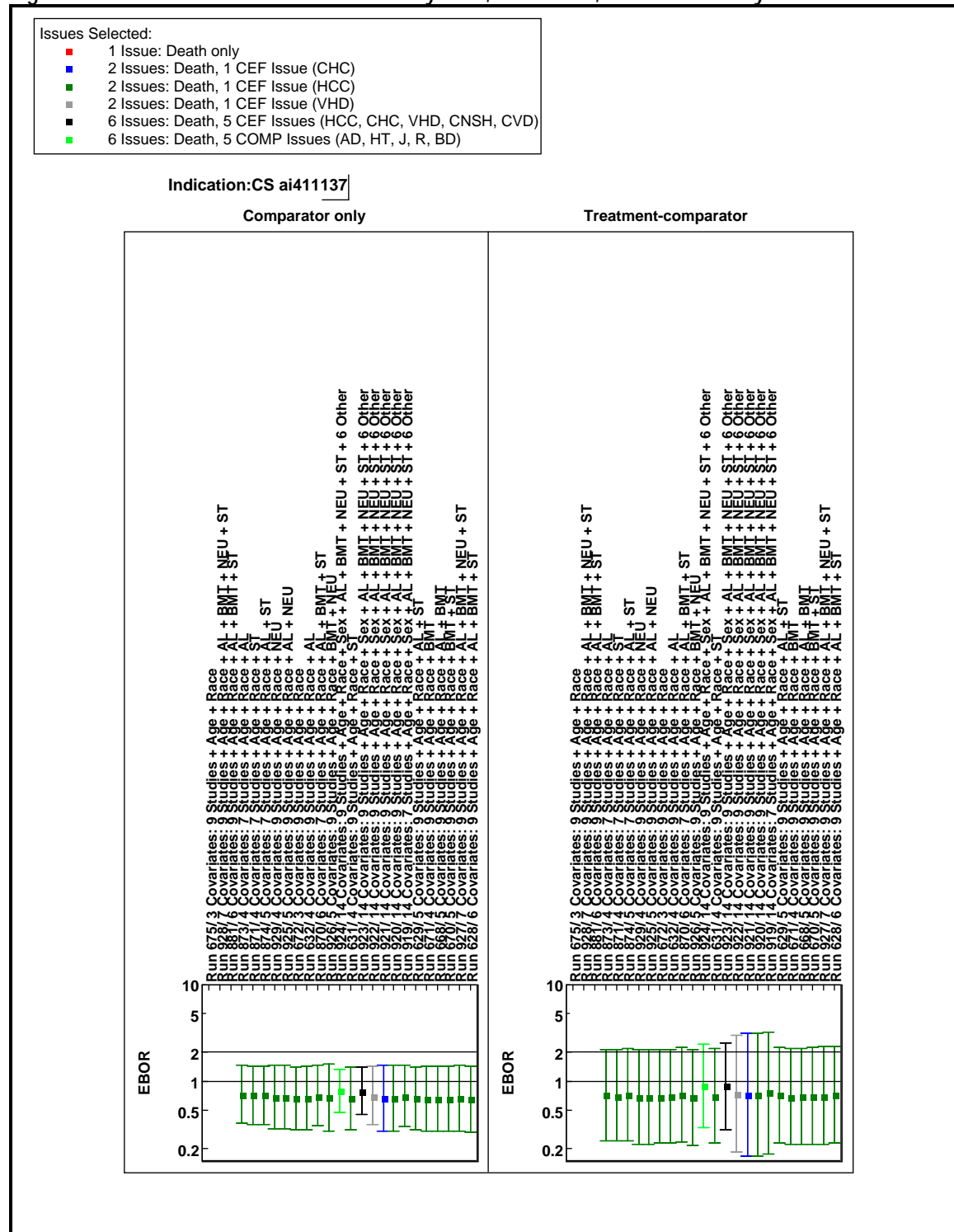
Figure 57: EBOR values for "CS ai411189" by runs, covariates, and issues analyzed
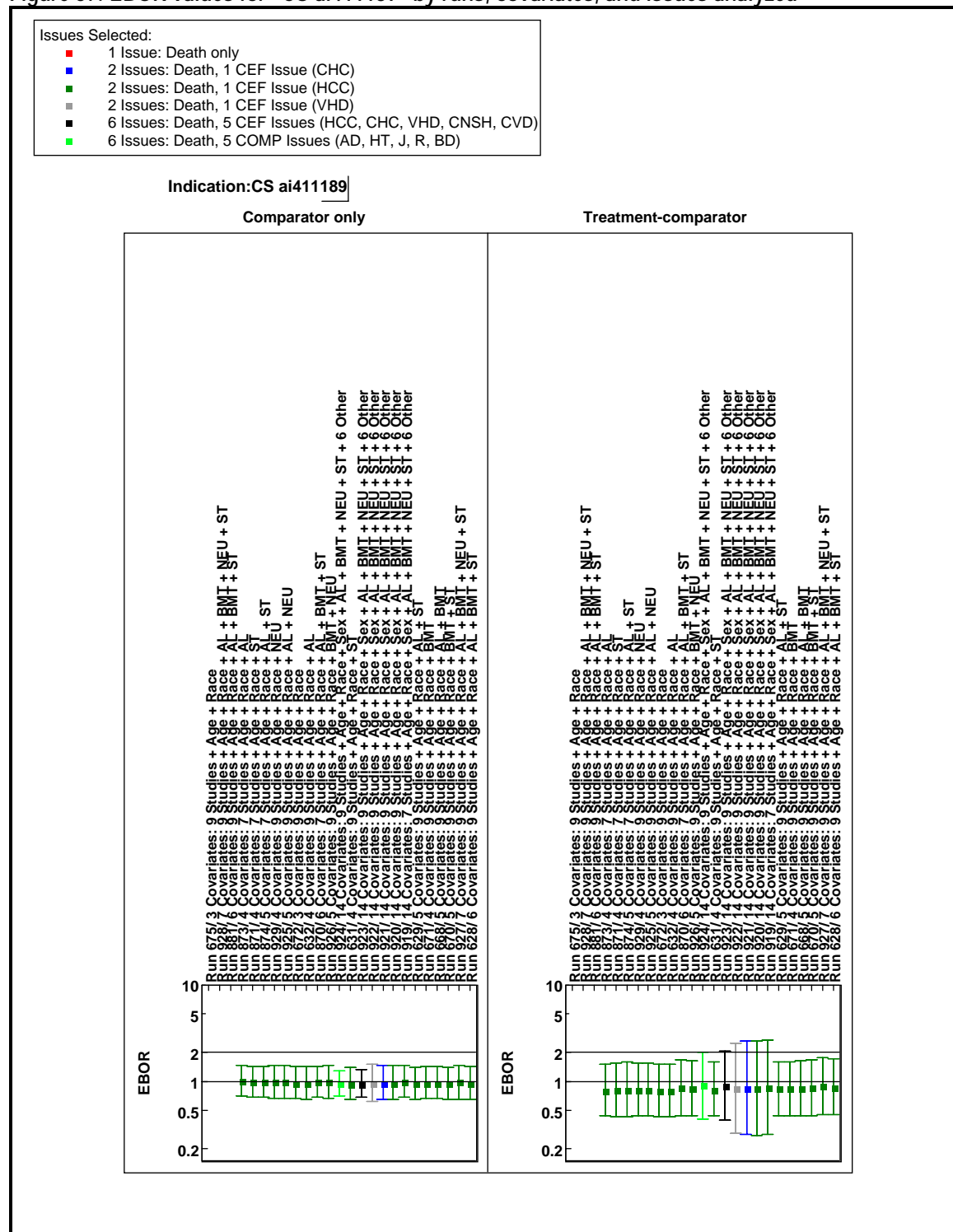
Figure 58: EBOR values for "CS ai411198" by runs, covariates, and issues analyzed
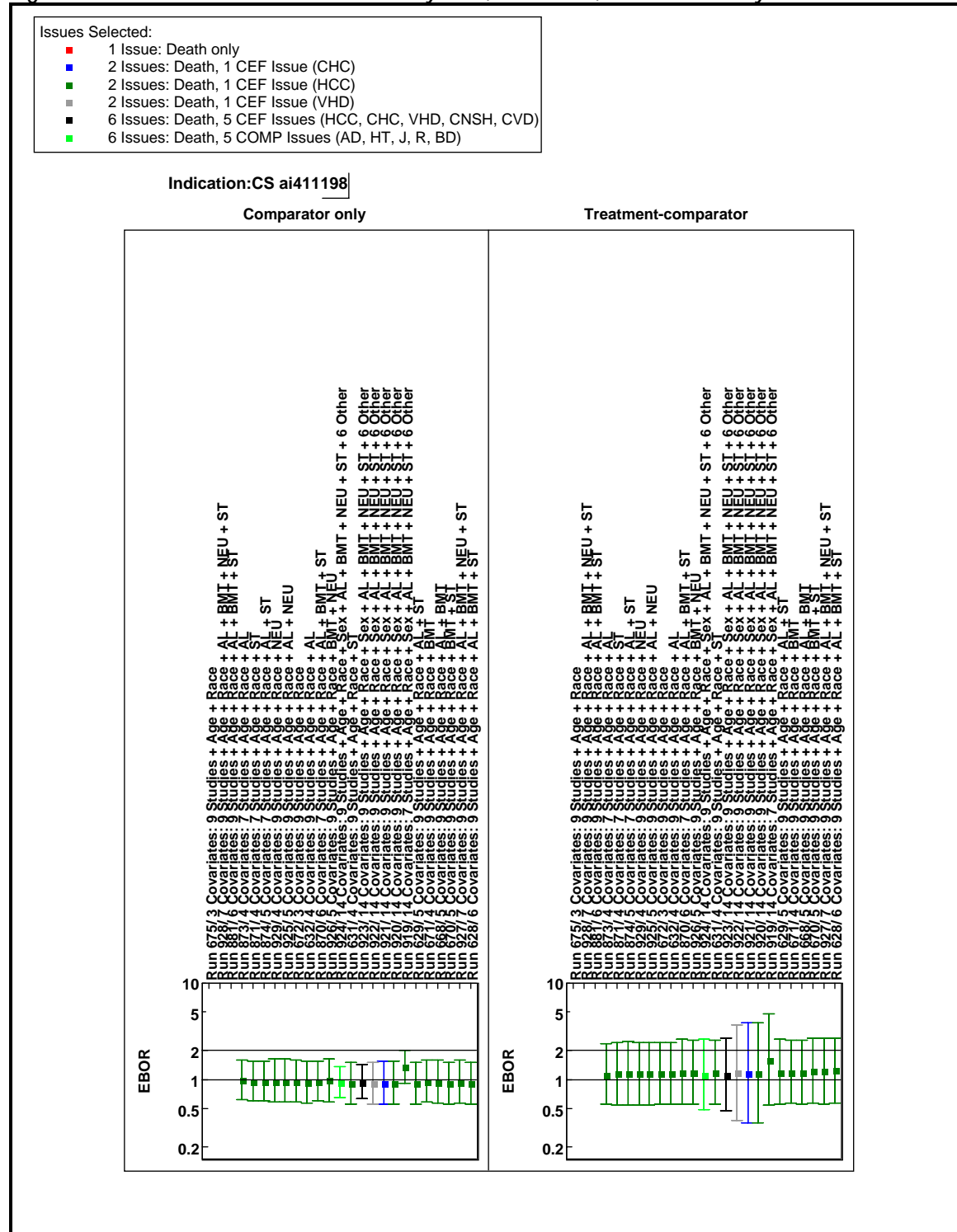
Figure 59: EBOR values for "CS ai411204" by runs, covariates, and issues analyzed
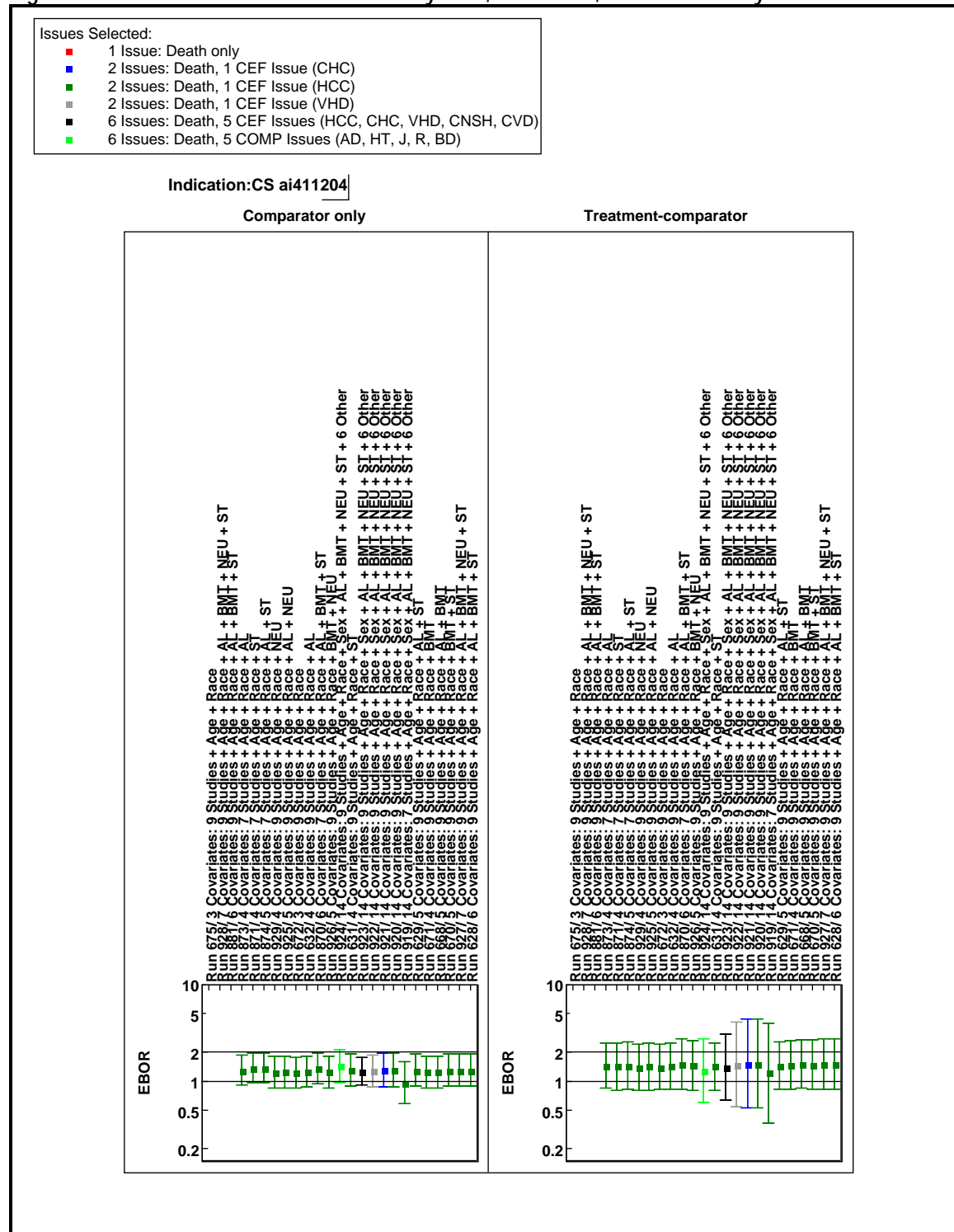
Figure 60: EBOR values for "NC ai411143" by runs, covariates, and issues analyzed
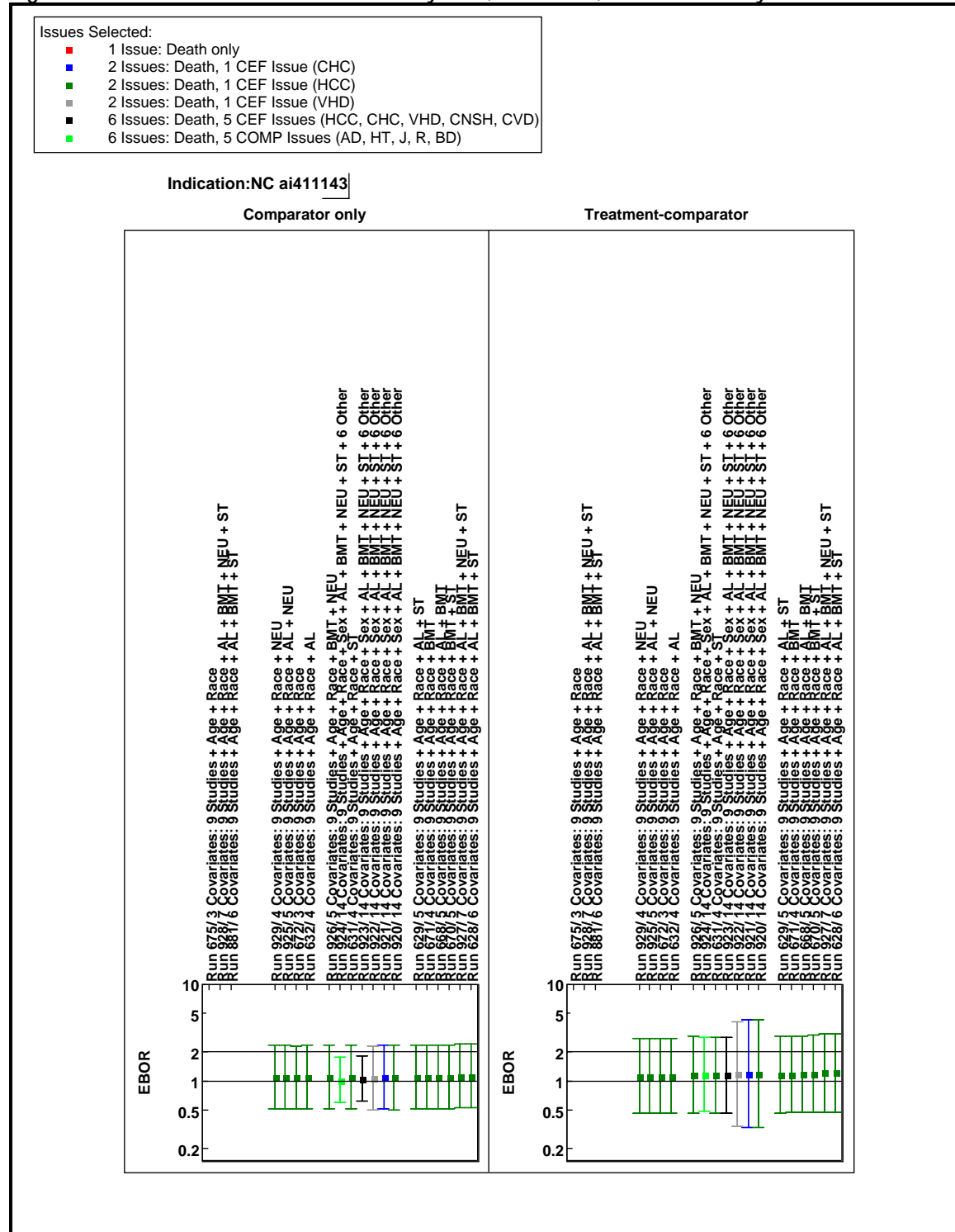
Figure 61: EBOR values for "NC ai411158" by runs, covariates, and issues analyzed
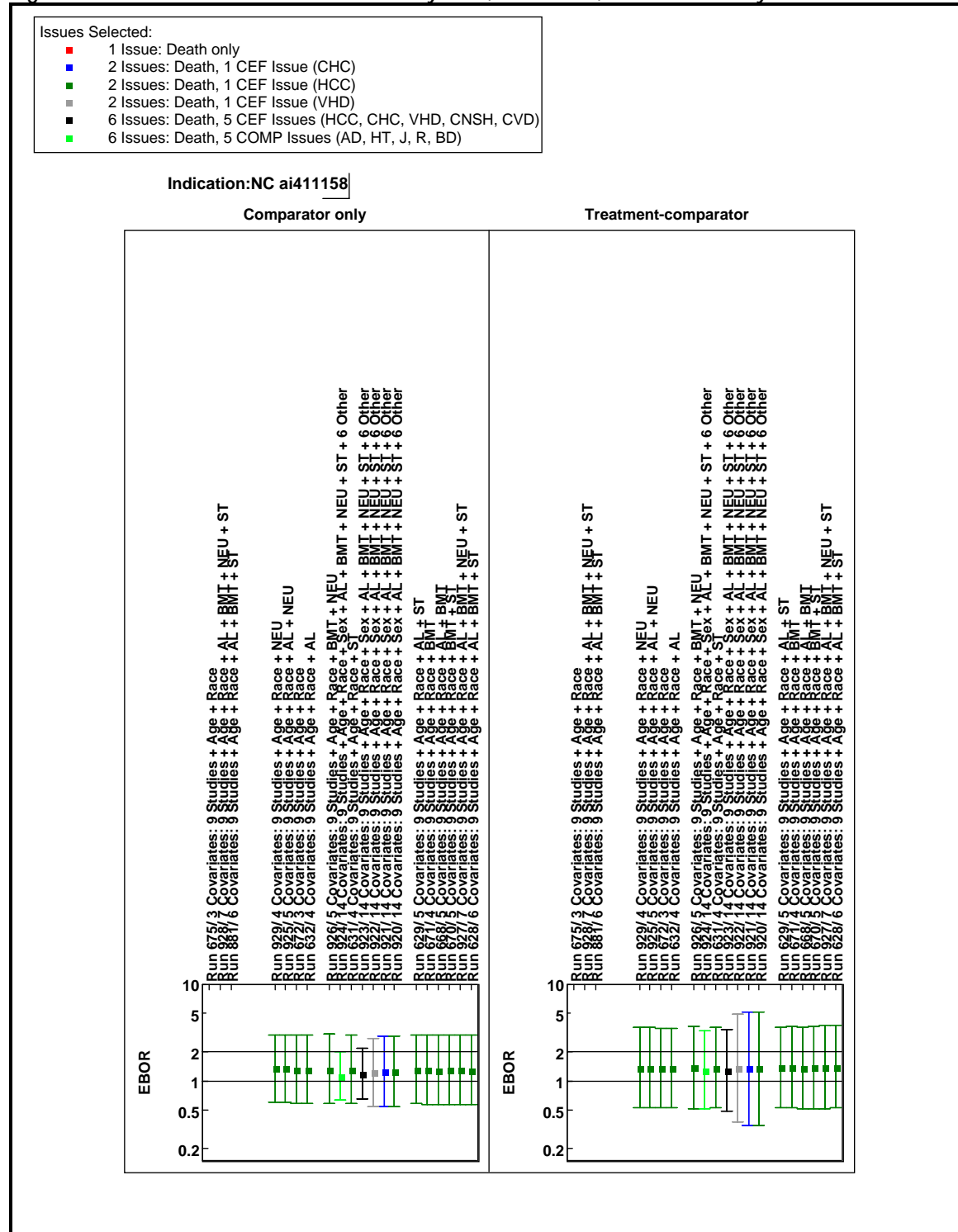
Figure 62: EBOR values for "Anti-microbial medication:Y" by runs, covariates, and issues analyzed

Issues Selected:
- ■ 1 Issue: Death only
- ■ 2 Issues: Death, 1 CEF Issue (CHC)
- ■ 2 Issues: Death, 1 CEF Issue (HCC)
- ■ 2 Issues: Death, 1 CEF Issue (VHD)
- ■ 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- ■ 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Anti-microbial medication:Y

Comparator only

Treatment-comparator
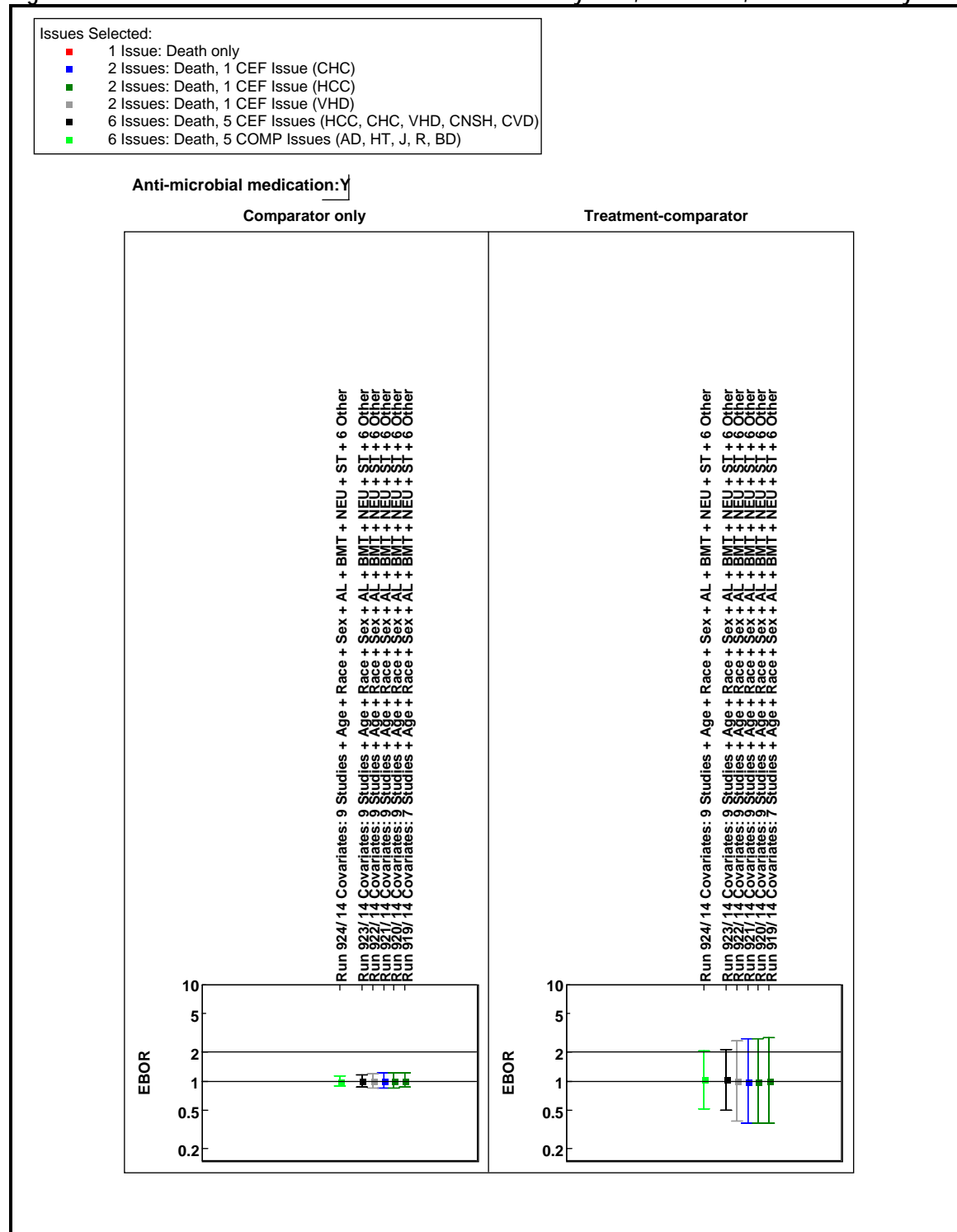
Figure 63: EBOR values for "Anti-microbial medication:N" by runs, covariates, and issues analyzed
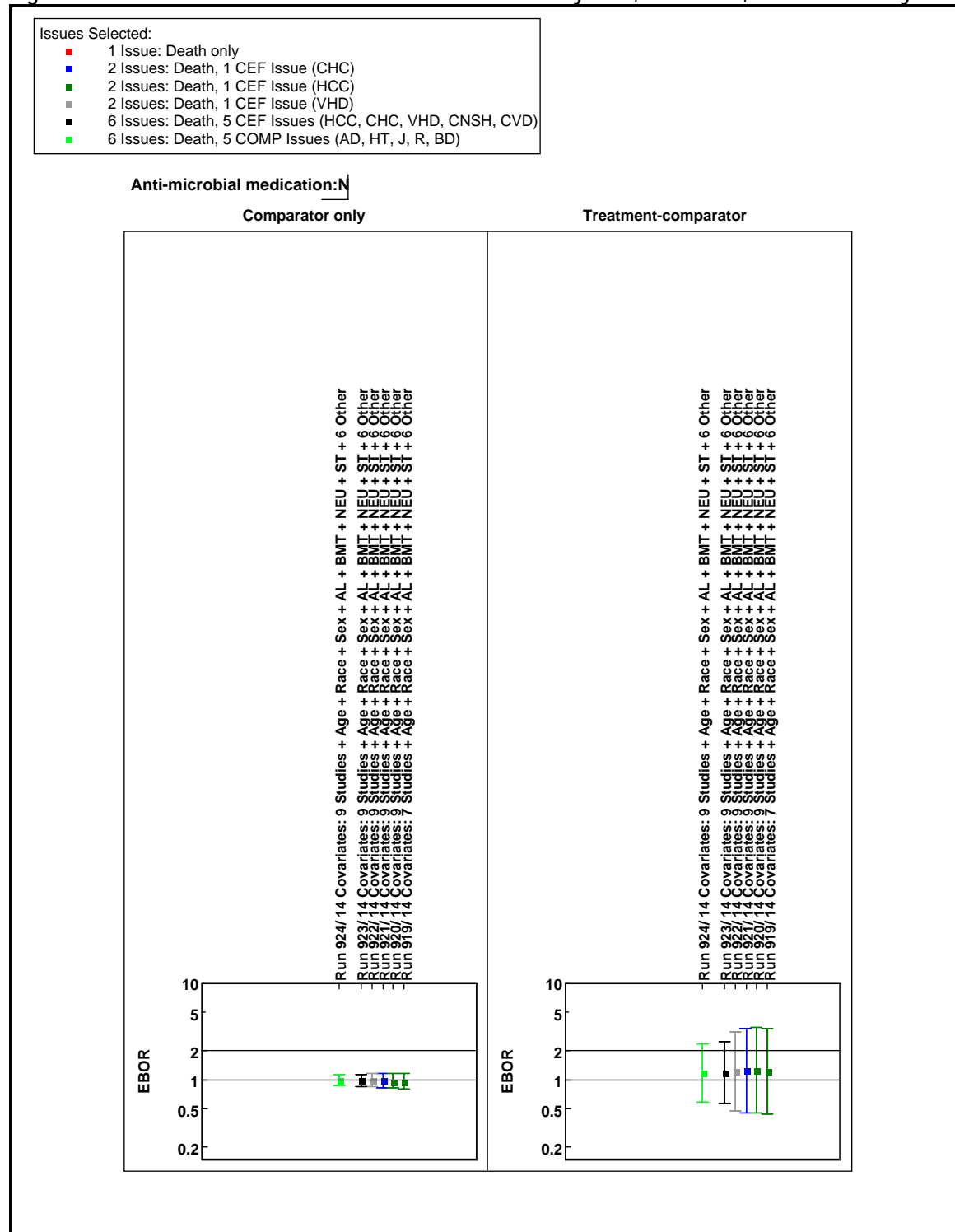
Figure 64: EBOR values for "Bone marrow transplant:Y" by runs, covariates, and issues analyzed
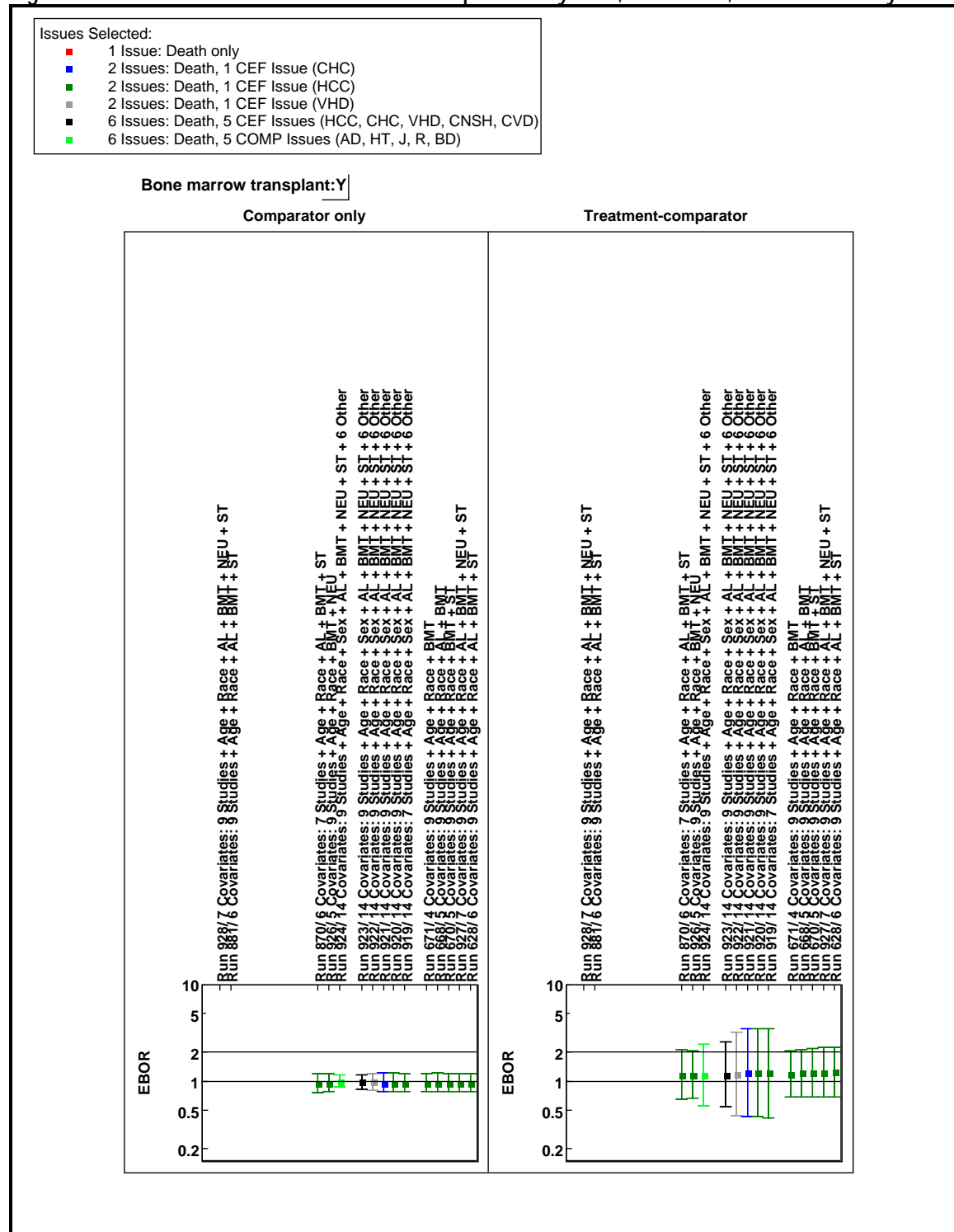
Figure 65: EBOR values for "Bone marrow transplant:N" by runs, covariates, and issues analyzed
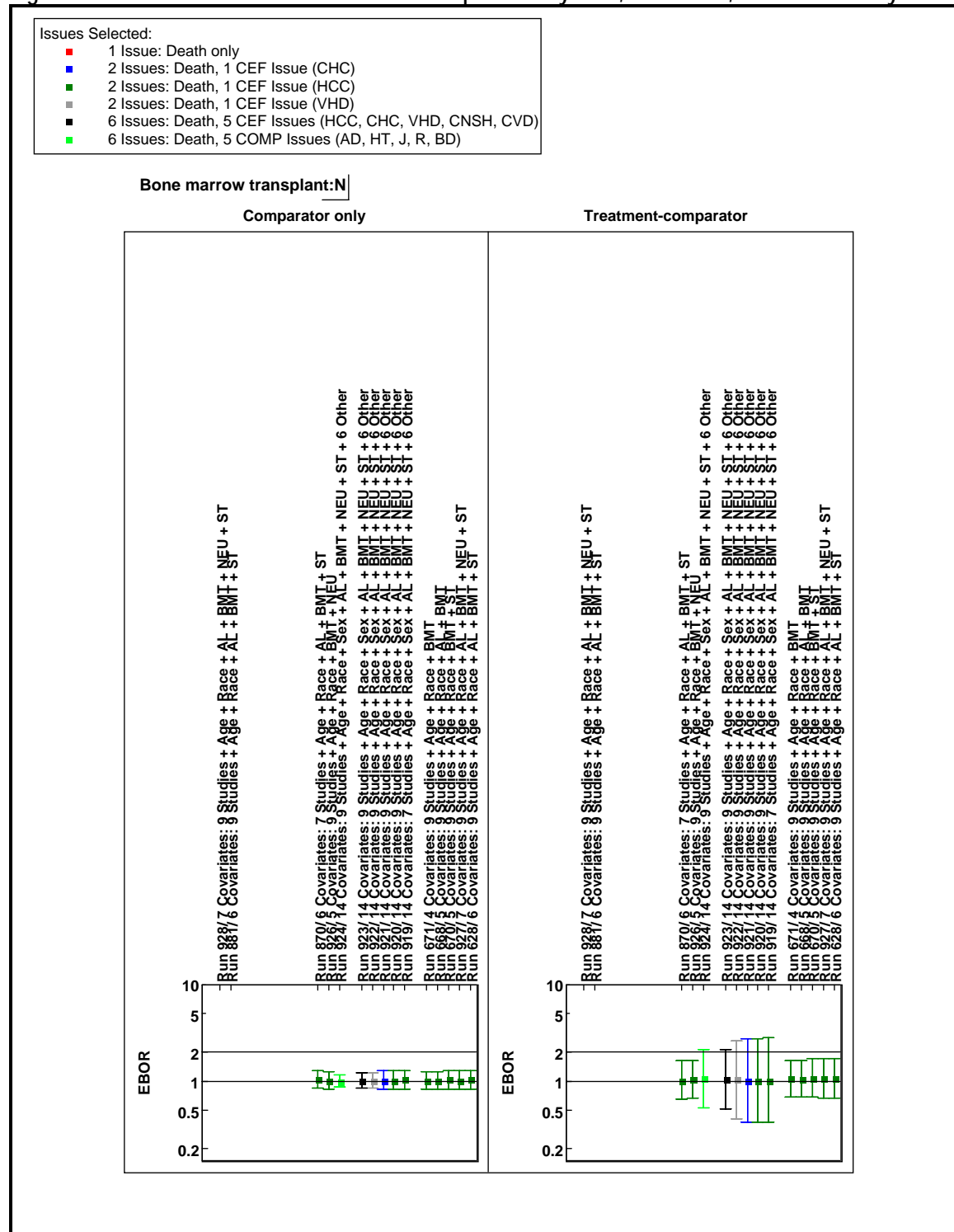
Figure 66: EBOR values for "Surgical procedure:Y" by runs, covariates, and issues analyzed
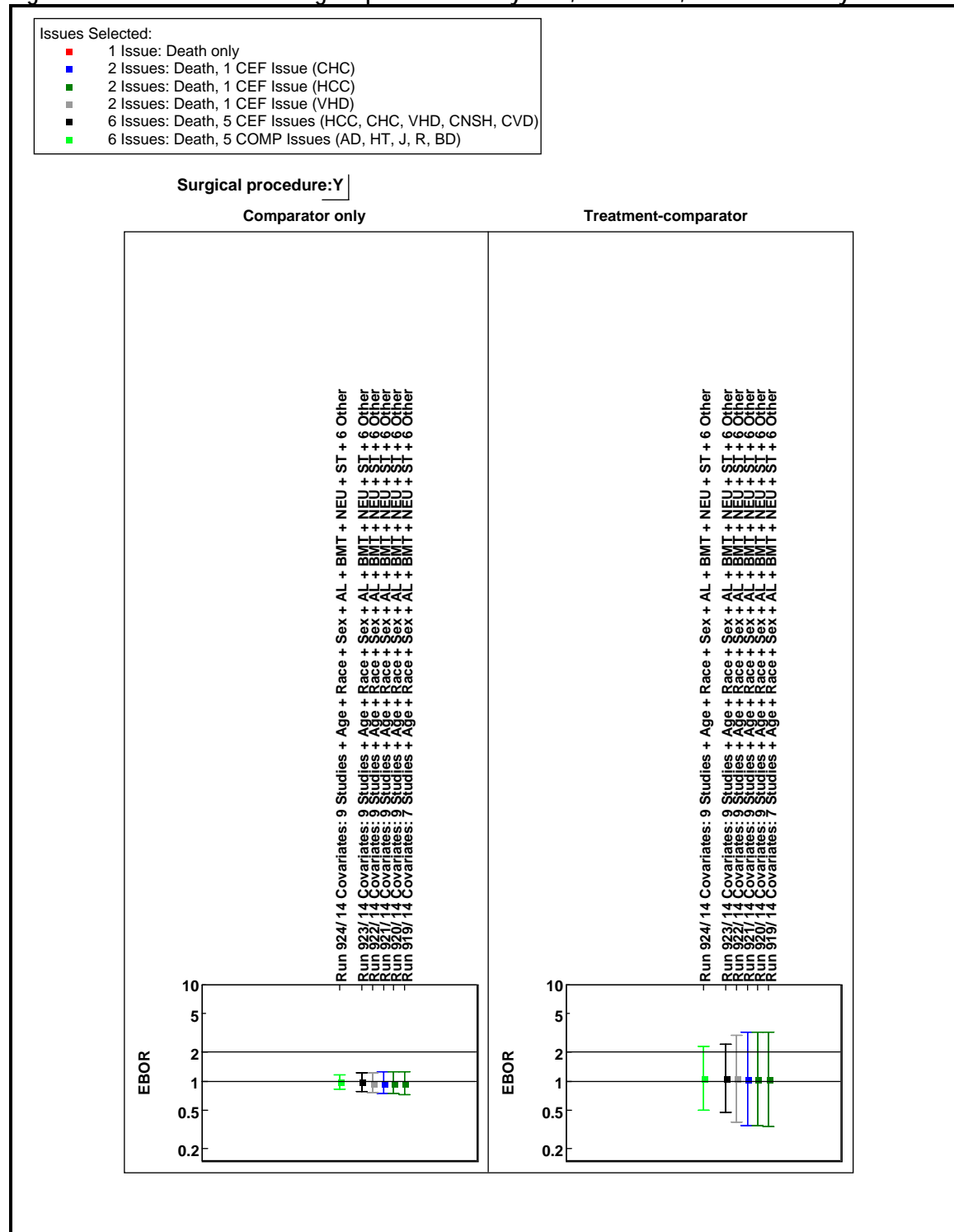
Figure 67: EBOR values for "Surgical procedure:N" by runs, covariates, and issues analyzed
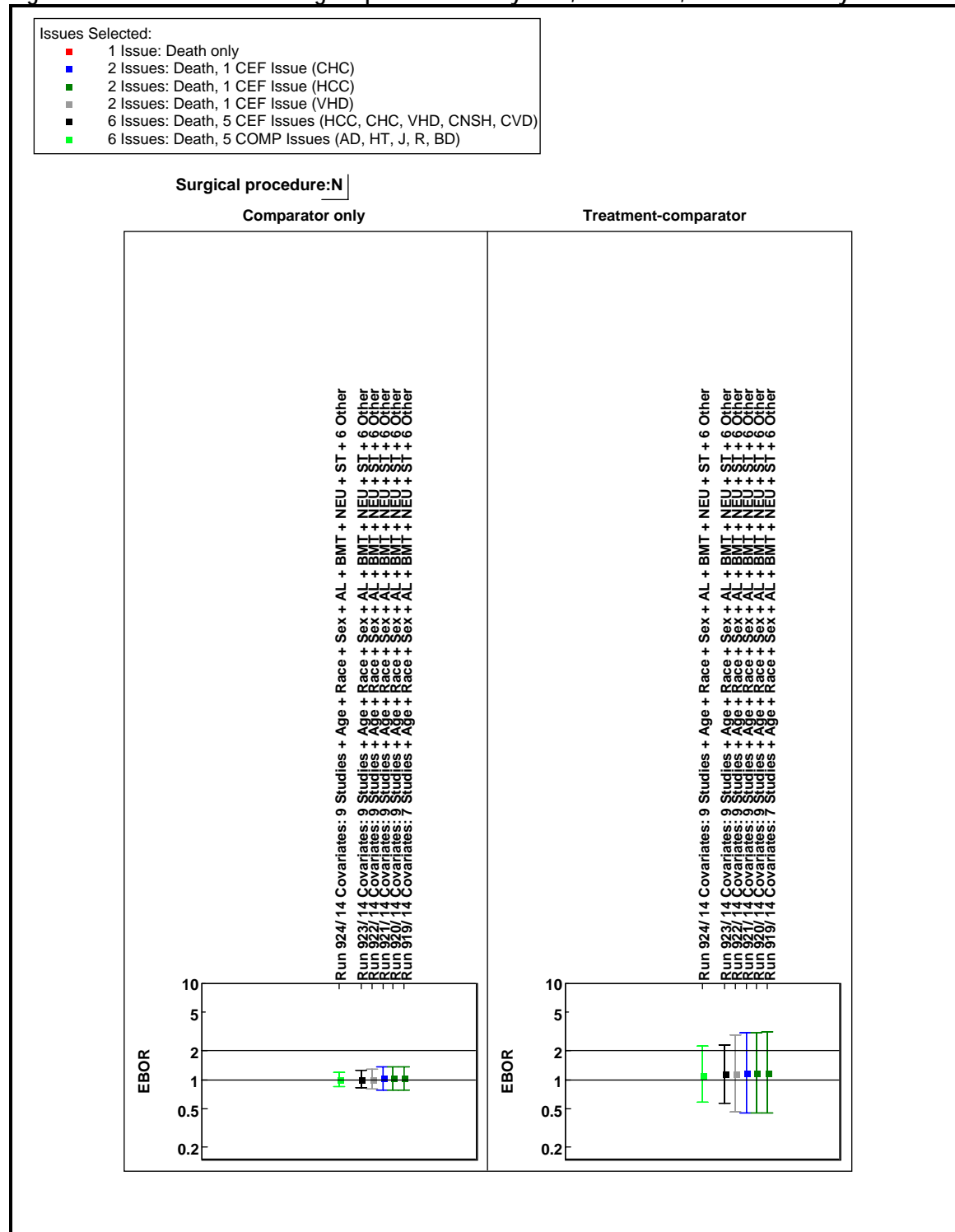
Figure 68: EBOR values for "Diabetes mellitus:Y" by runs, covariates, and issues analyzed

Issues Selected:
- 🟥 1 Issue: Death only
- 🟦 2 Issues: Death, 1 CEF Issue (CHC)
- 🟩 2 Issues: Death, 1 CEF Issue (HCC)
- ⬜ 2 Issues: Death, 1 CEF Issue (VHD)
- ⬛ 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- 🟩 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Diabetes mellitus:Y

Comparator only

Treatment-comparator
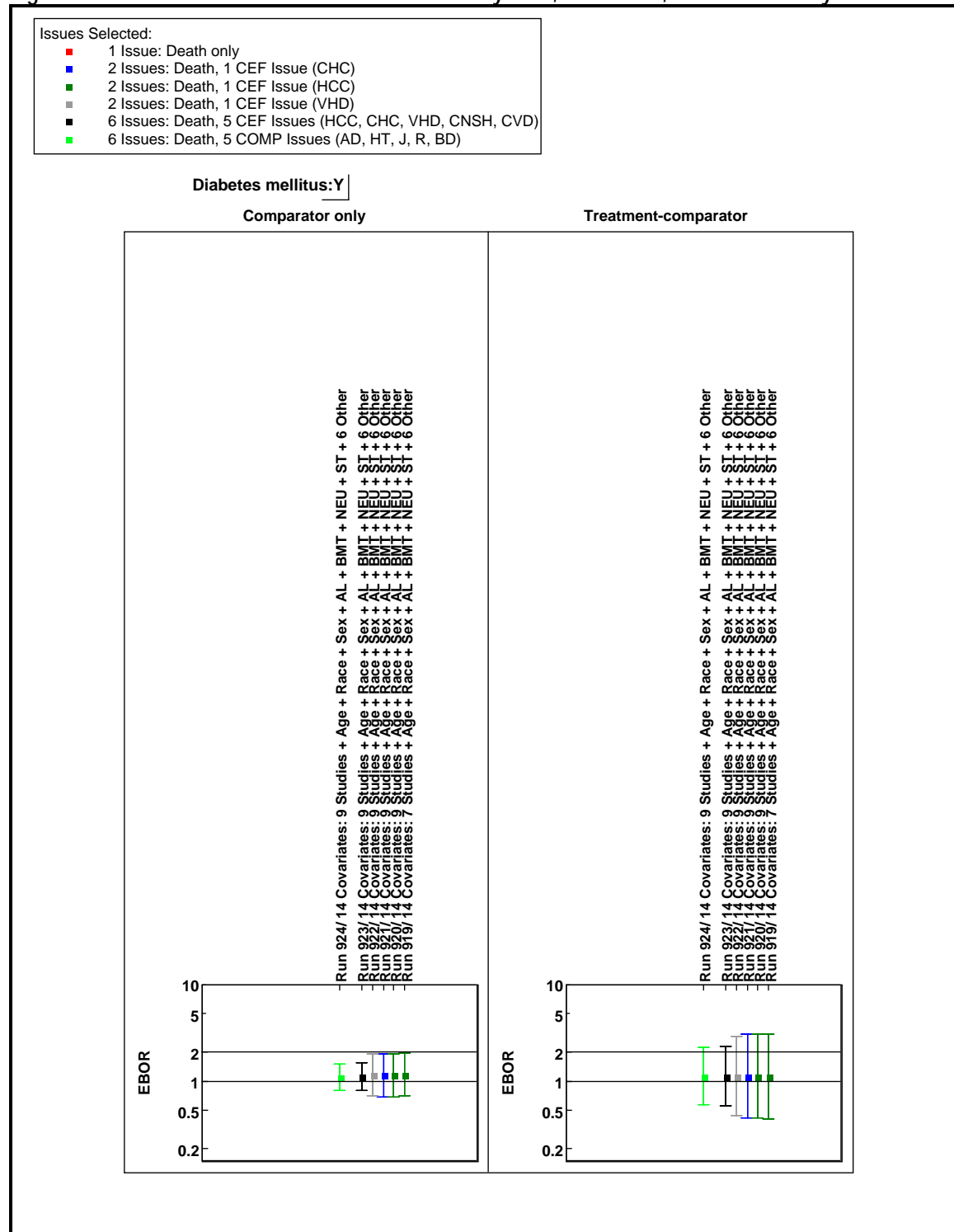
Figure 69: EBOR values for "Diabetes mellitus:N" by runs, covariates, and issues analyzed
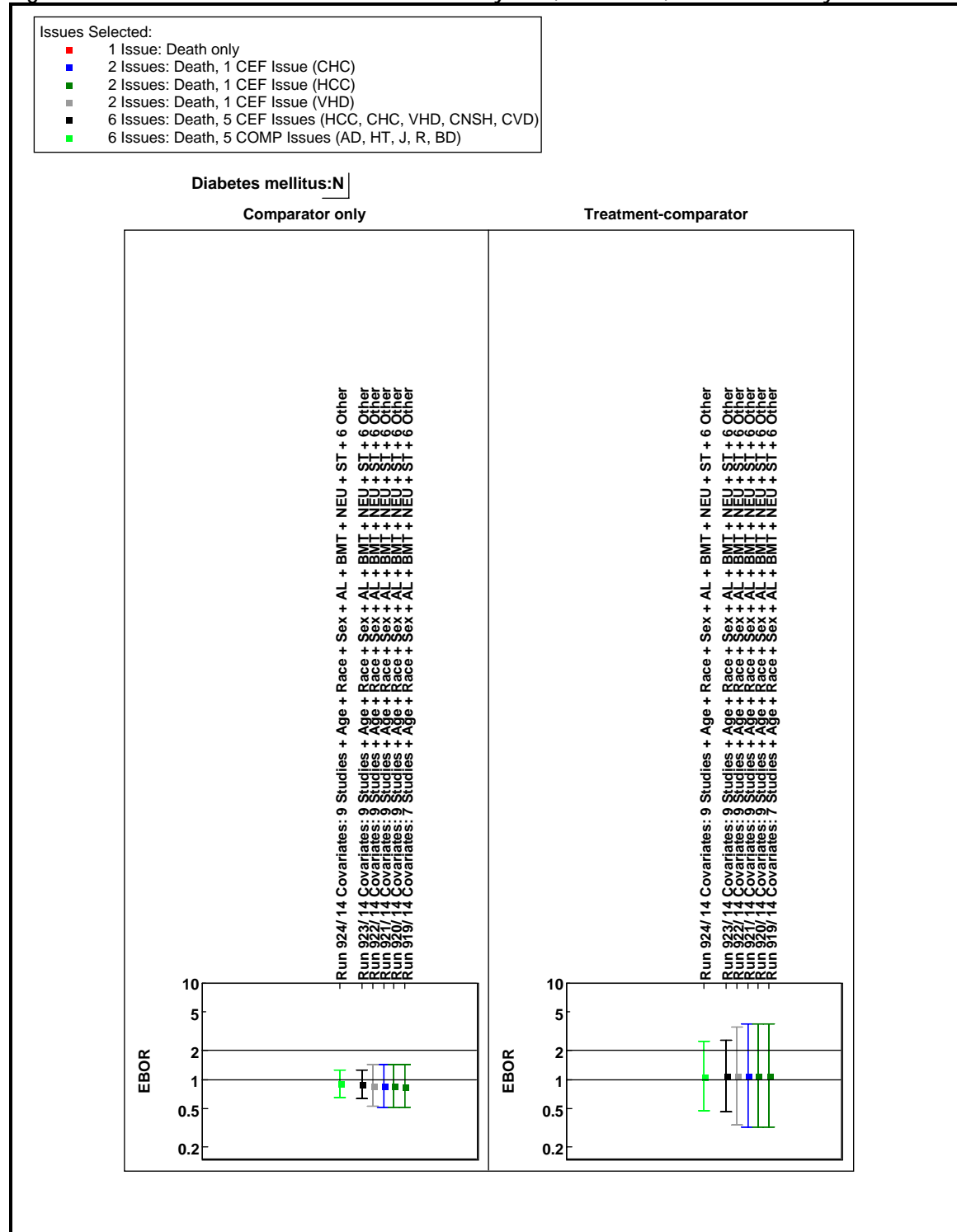
Figure 70: EBOR values for "Renal impairment:Y" by runs, covariates, and issues analyzed
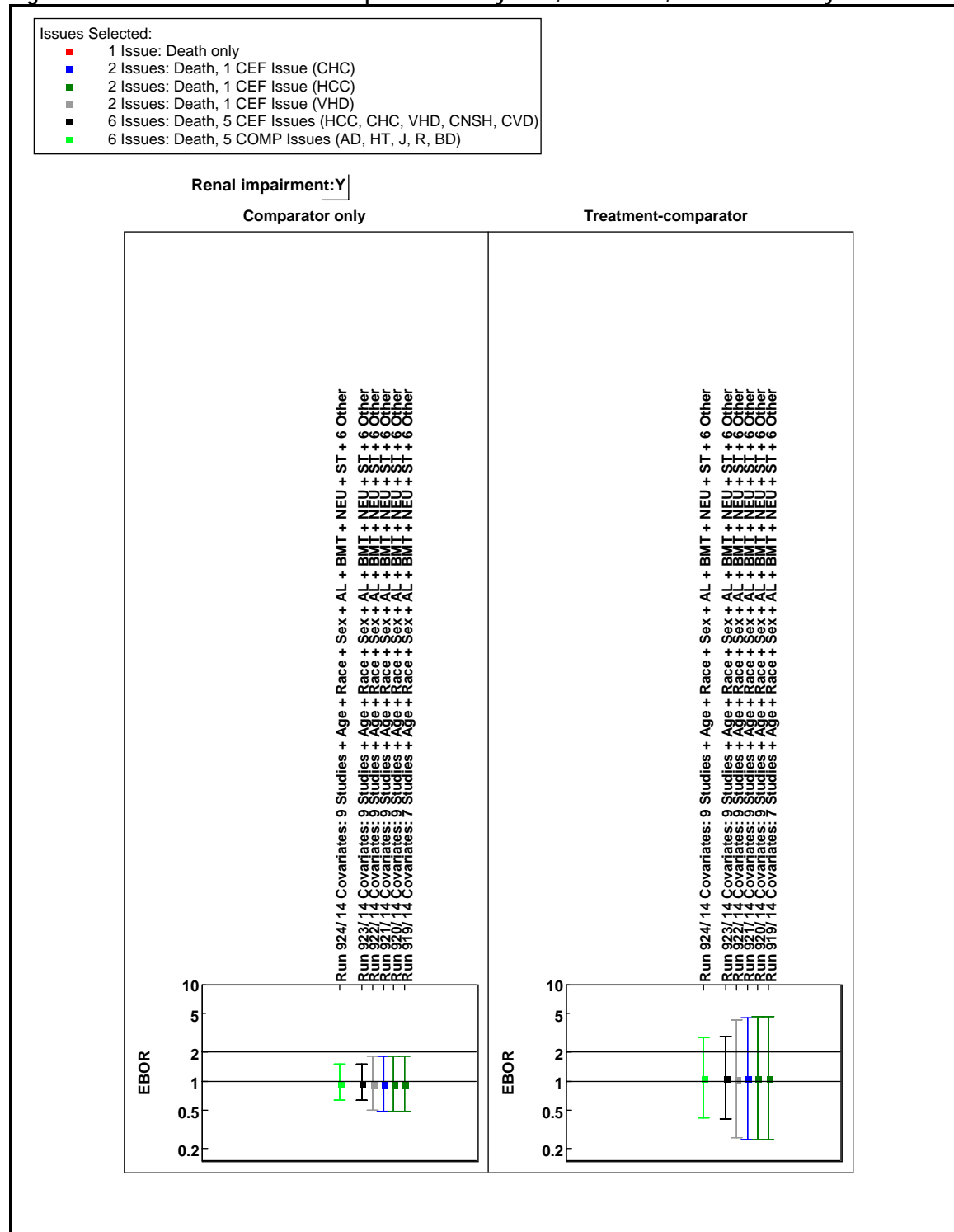
Figure 71: EBOR values for "Renal impairment:N" by runs, covariates, and issues analyzed
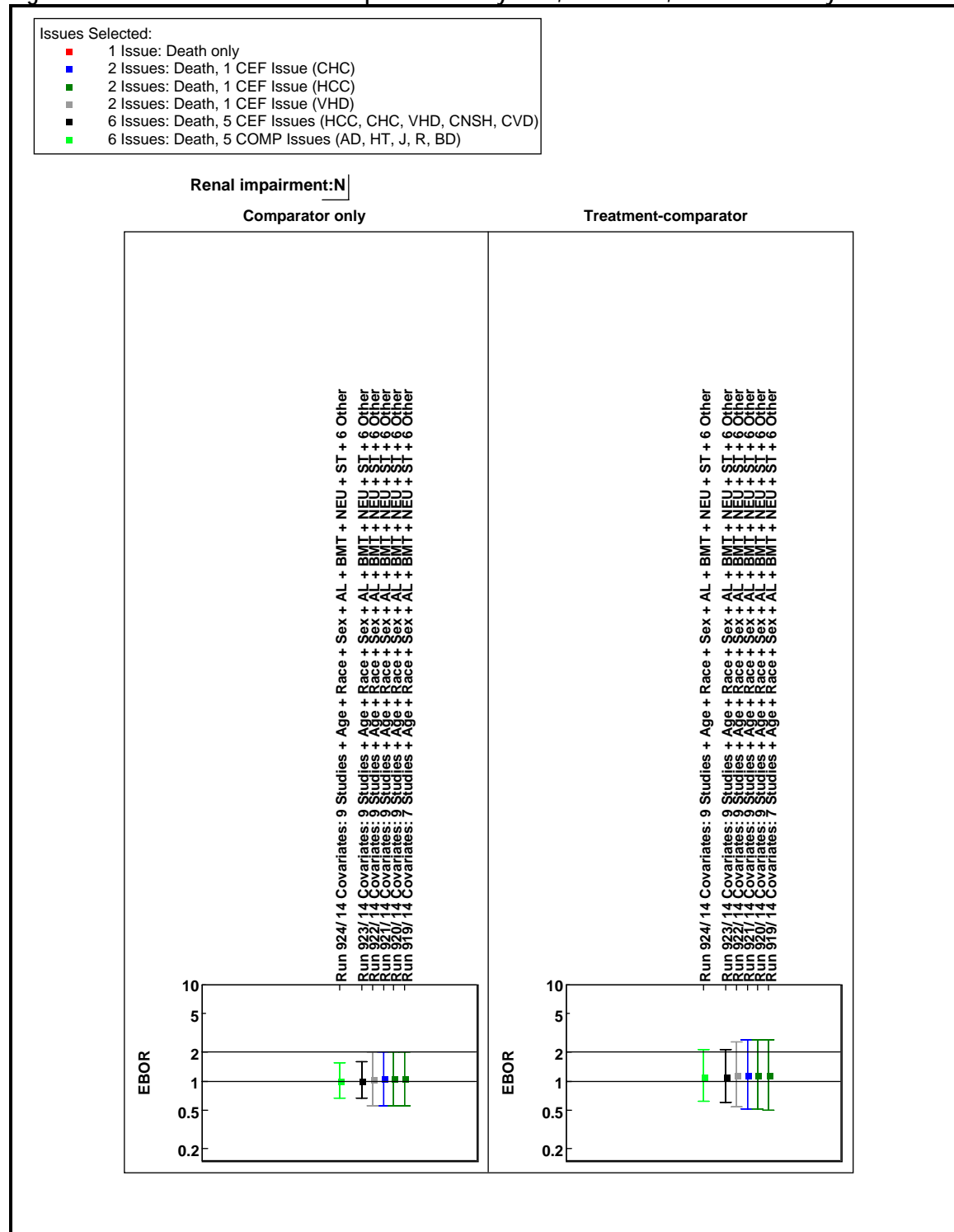
Figure 72: EBOR values for "Lymphoma/multiple myeloma:Y" by runs, covariates, and issues analyzed
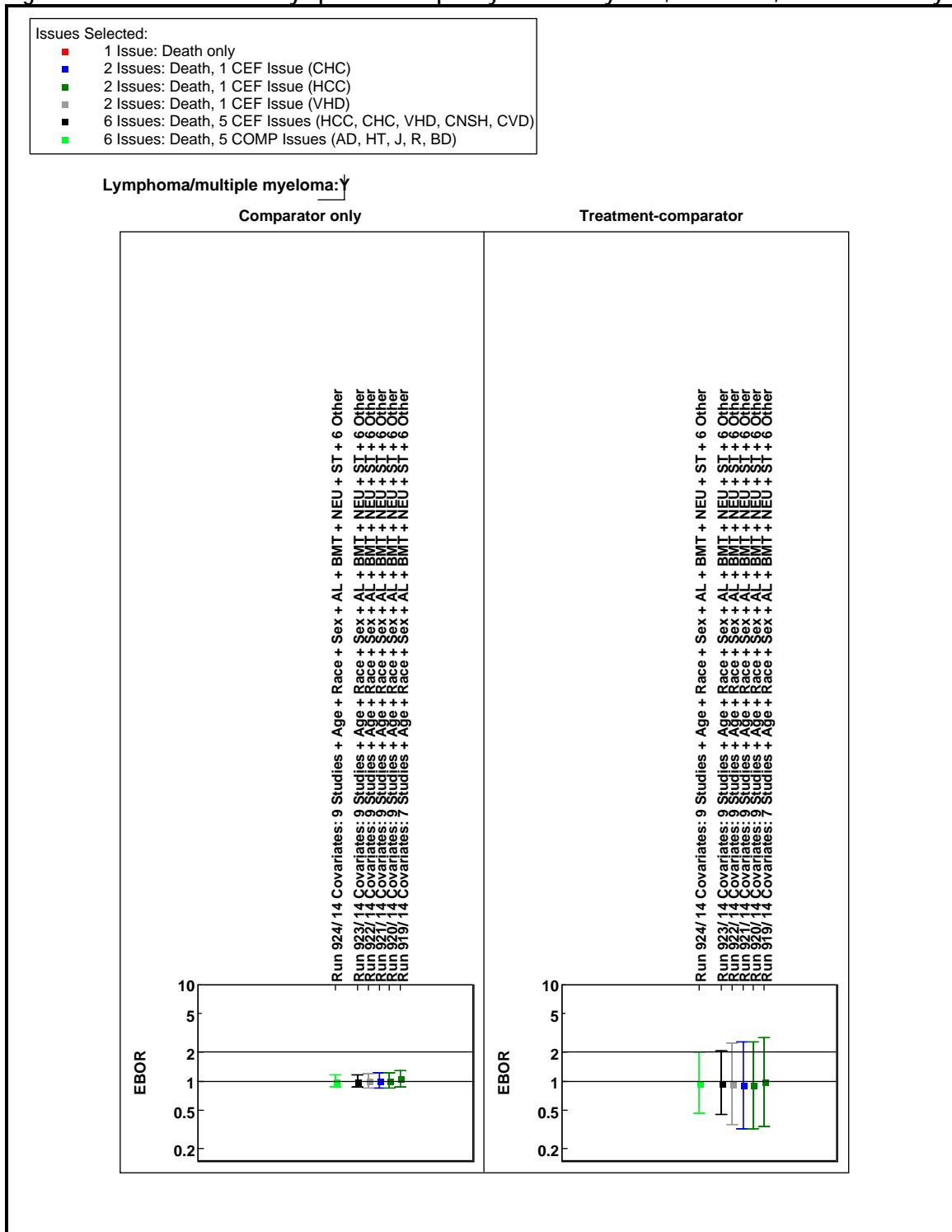
Figure 73: EBOR values for "Lymphoma/multiple myeloma:N" by runs, covariates, and issues analyzed

Issues Selected:
- 1 Issue: Death only
- 2 Issues: Death, 1 CEF Issue (CHC)
- 2 Issues: Death, 1 CEF Issue (HCC)
- 2 Issues: Death, 1 CEF Issue (VHD)
- 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Lymphoma/multiple myeloma:N

Figure 74: EBOR values for "Solid tumor:Y" by runs, covariates, and issues analyzed
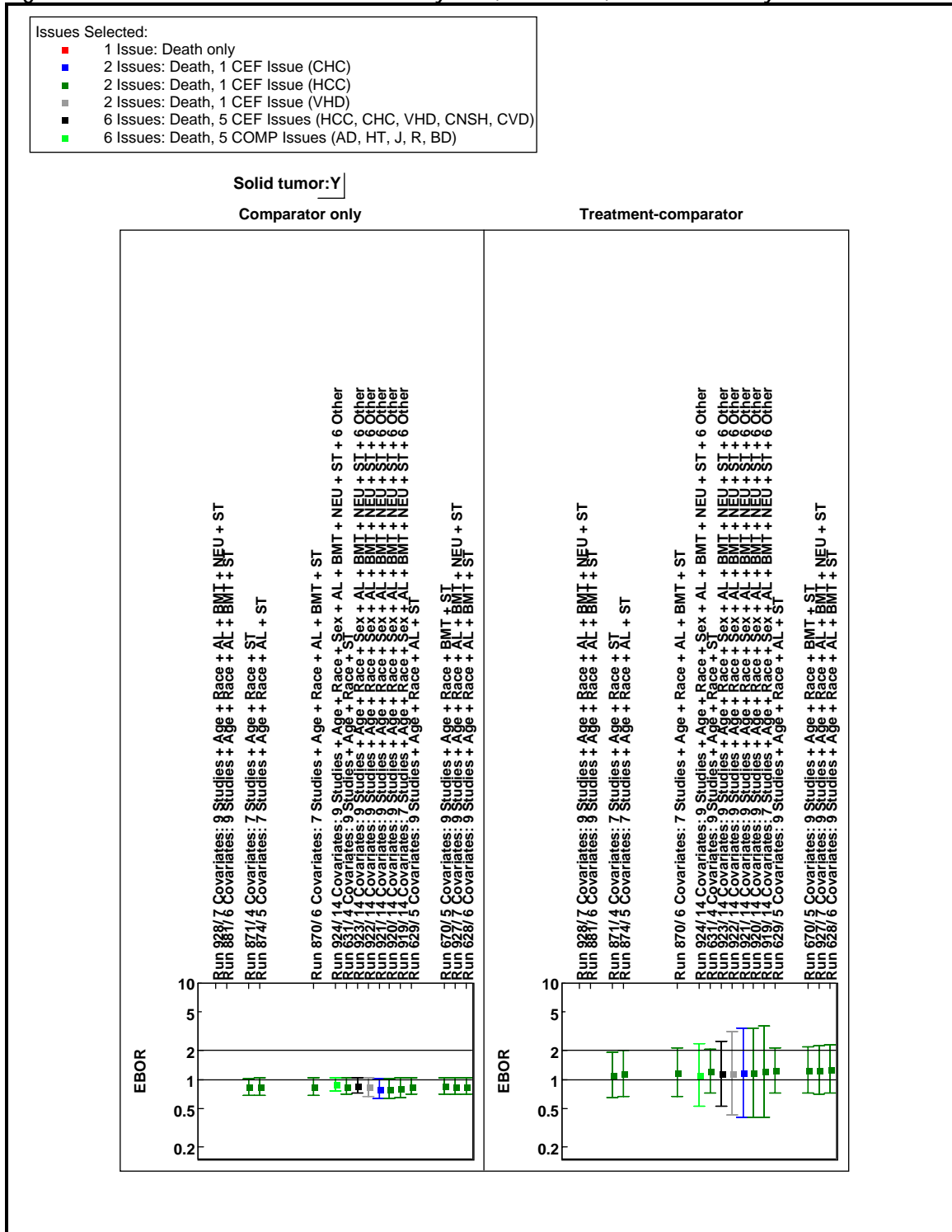
Figure 75: EBOR values for "Solid tumor:N" by runs, covariates, and issues analyzed
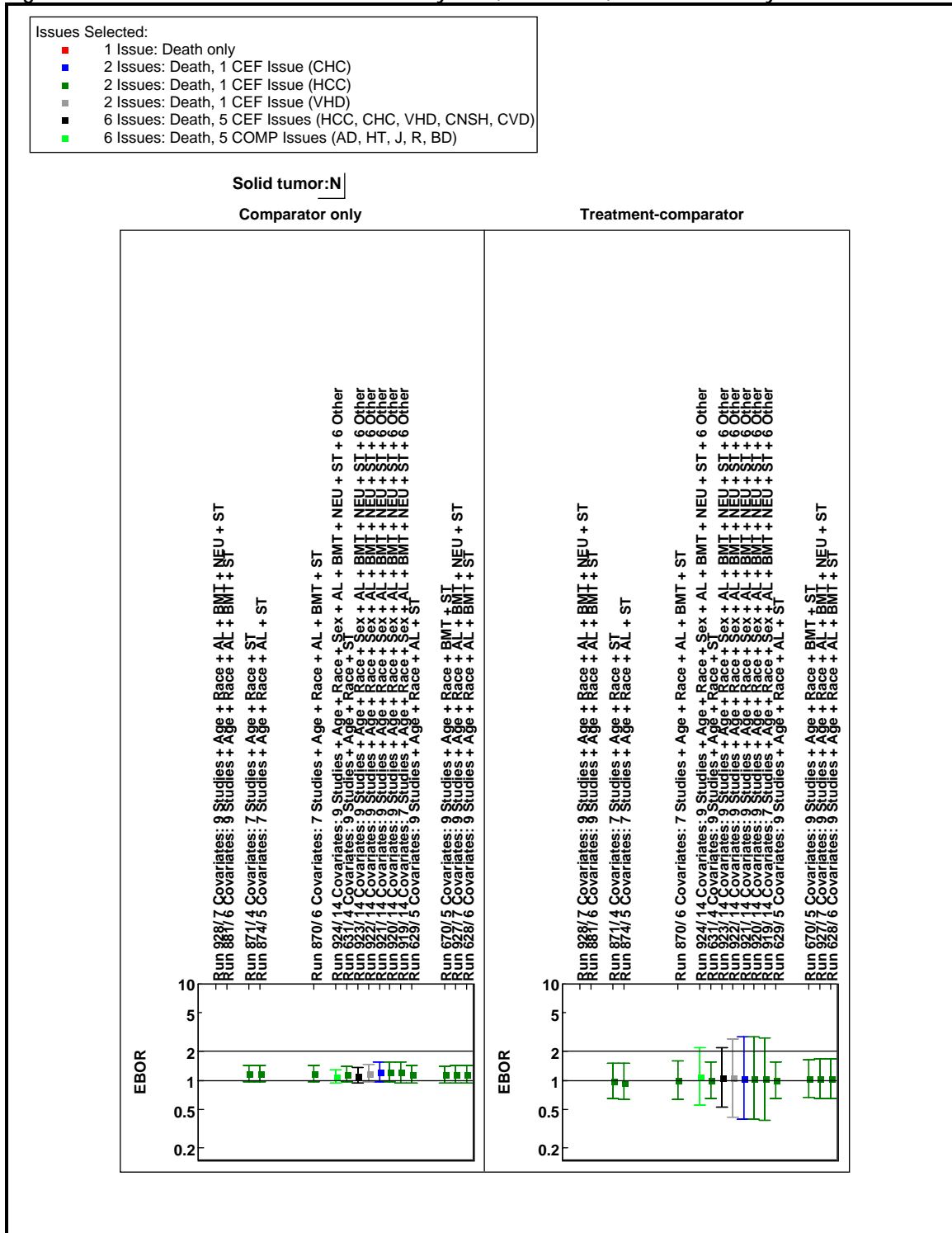
Figure 76: EBOR values for "Acute leukemia:Y" by runs, covariates, and issues analyzed
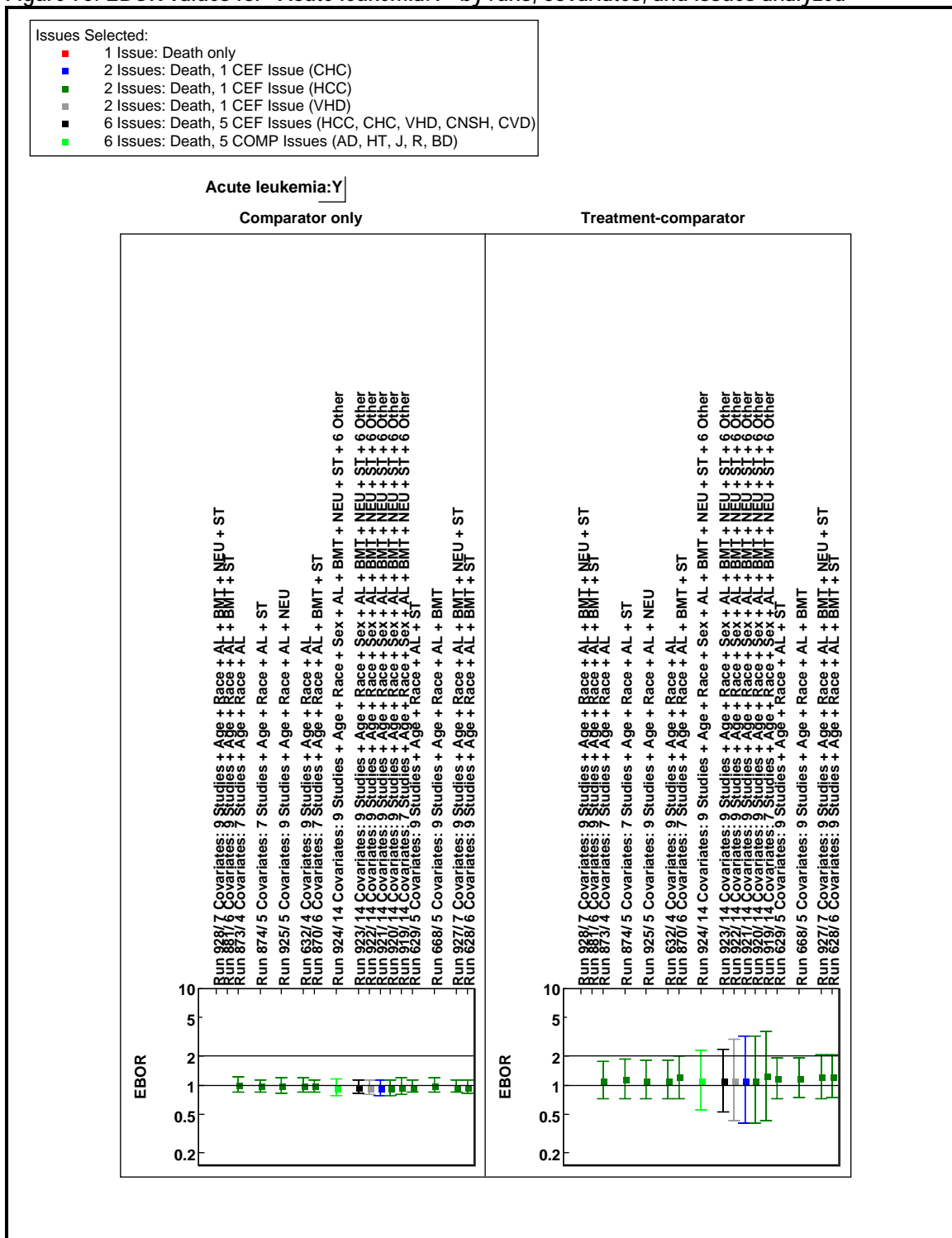
Figure 77: EBOR values for "Acute leukemia:N" by runs, covariates, and issues analyzed

Figure 78: EBOR values for "Age:<=17" by runs, covariates, and issues analyzed

Issues Selected:
- 🟥 1 Issue: Death only
- 🟦 2 Issues: Death, 1 CEF Issue (CHC)
- 🟩 2 Issues: Death, 1 CEF Issue (HCC)
- ⬜ 2 Issues: Death, 1 CEF Issue (VHD)
- ⬛ 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- 🟢 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Age:<=17

Figure 79: EBOR values for "Age:<=40" by runs, covariates, and issues analyzed
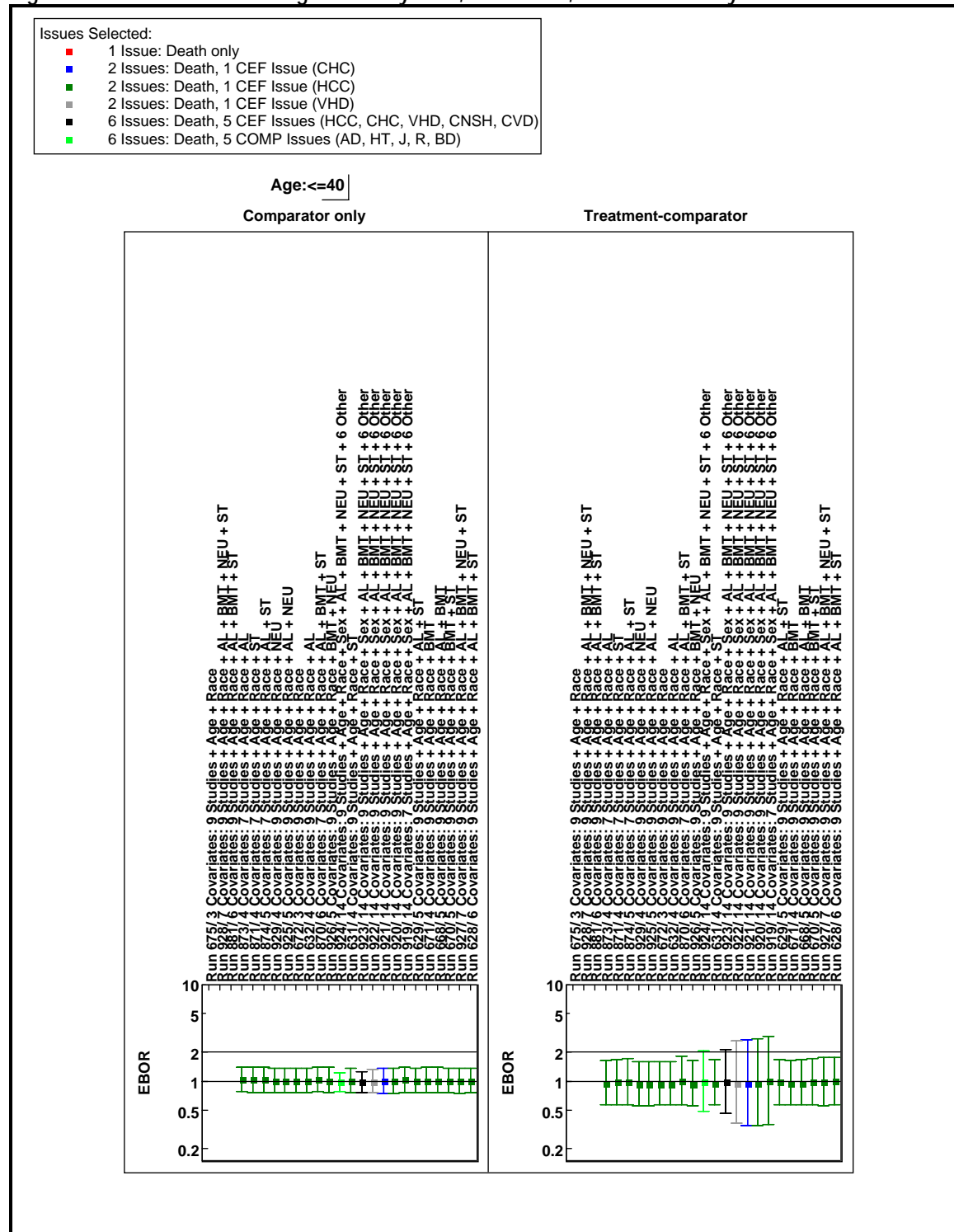
Figure 80: EBOR values for "Age:<=60" by runs, covariates, and issues analyzed
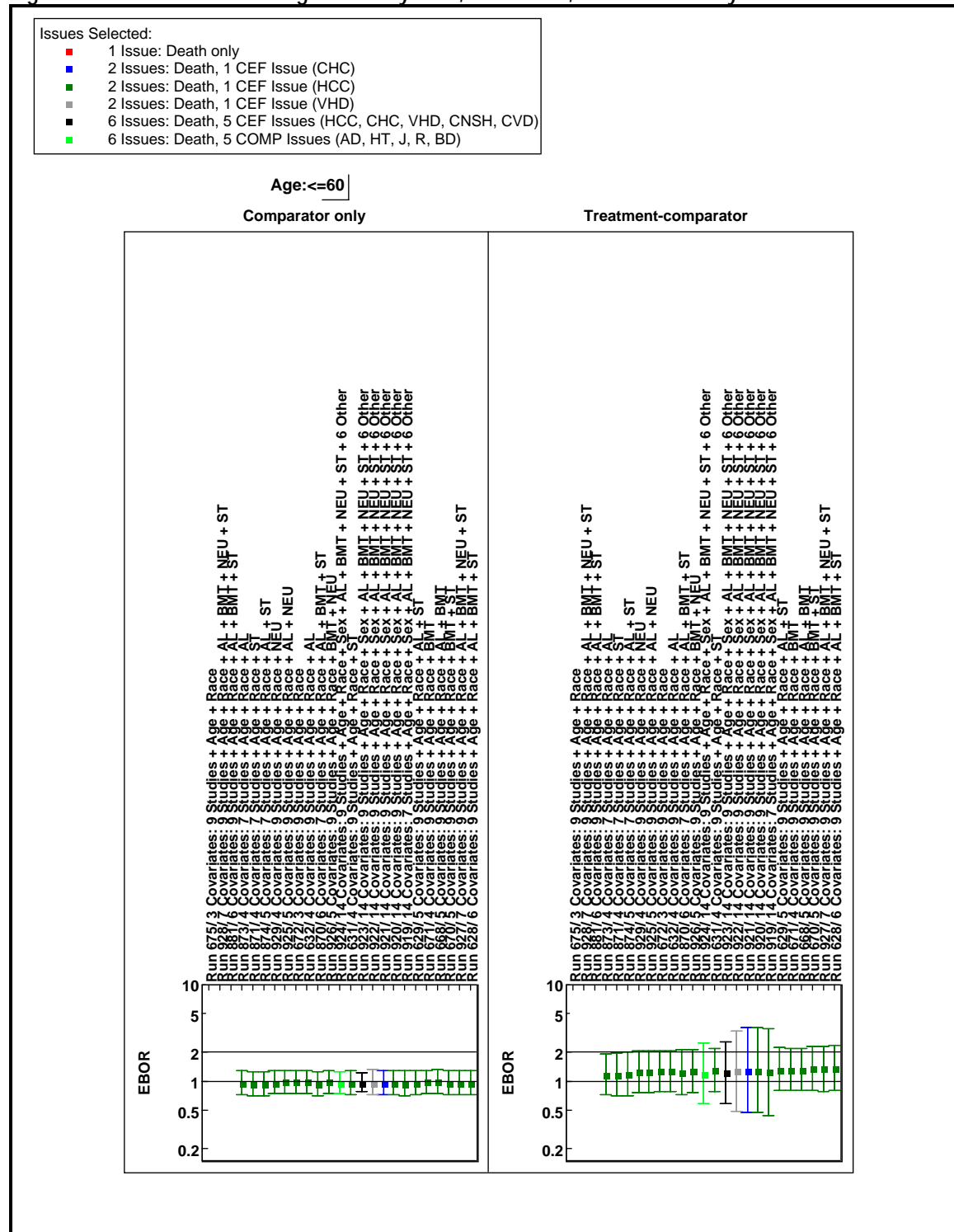
Figure 81: EBOR values for "Age:>60" by runs, covariates, and issues analyzed

Issues Selected:
- ■ 1 Issue: Death only
- ■ 2 Issues: Death, 1 CEF Issue (CHC)
- ■ 2 Issues: Death, 1 CEF Issue (HCC)
- ■ 2 Issues: Death, 1 CEF Issue (VHD)
- ■ 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- ■ 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)

Age:>60

Comparator only

Treatment-comparator
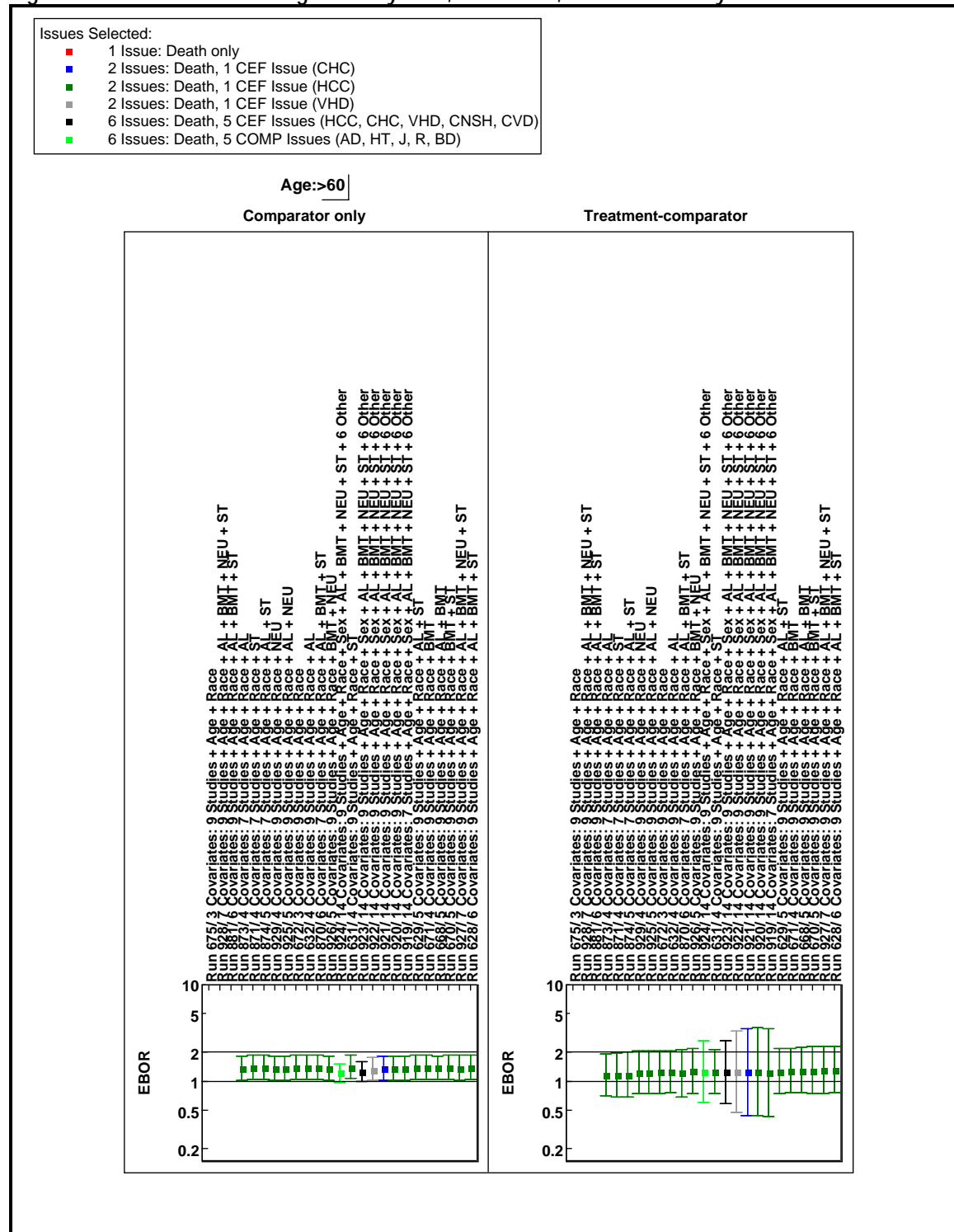
Figure 82: EBOR values for "Creatinine (2):<=2.5" by runs, covariates, and issues analyzed
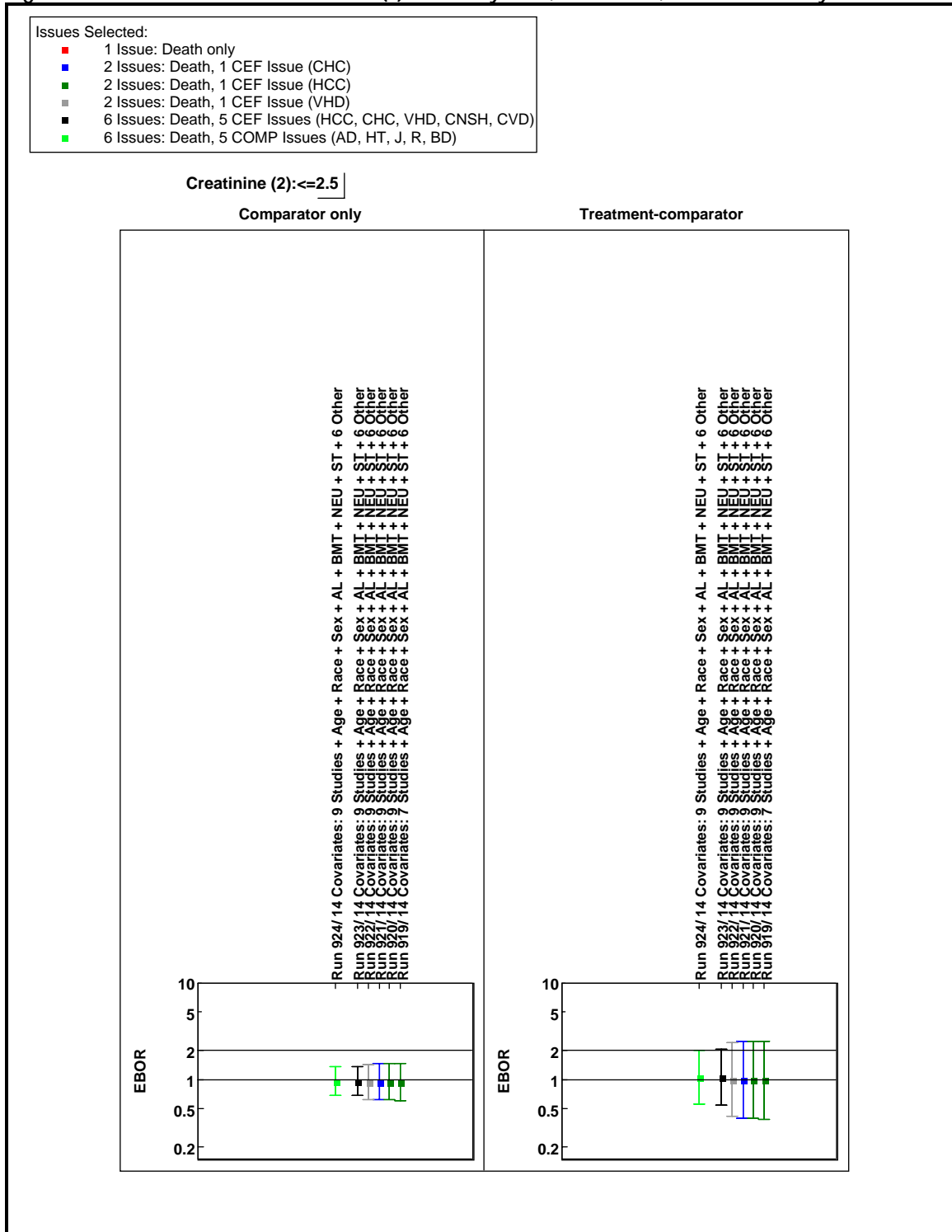
Figure 83: EBOR values for "Creatinine (2):>2.5" by runs, covariates, and issues analyzed
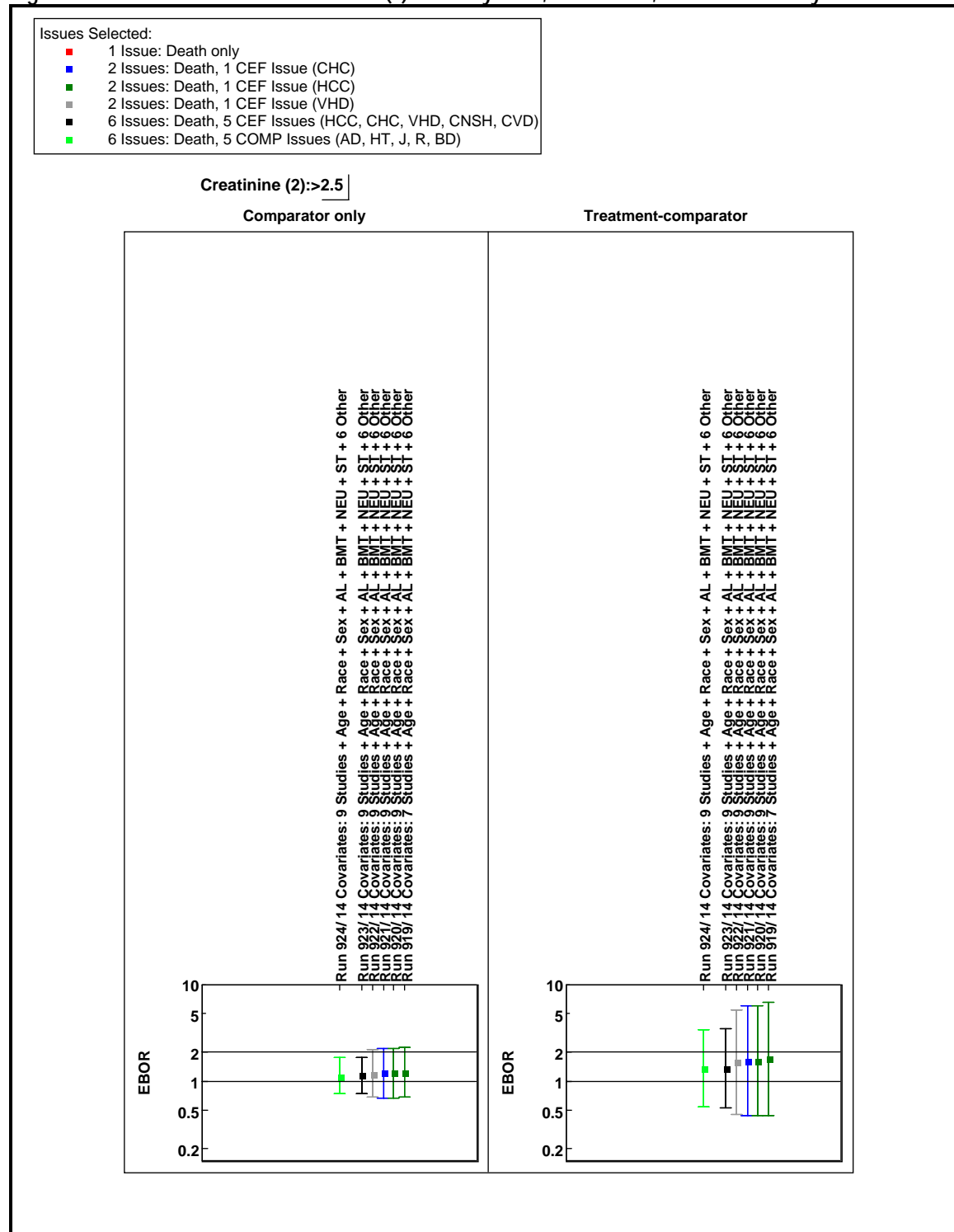
Figure 84: EBOR values for "Creatinine (2):Not Specified" by runs, covariates, and issues analyzed

Issues Selected:
- ■ 1 Issue: Death only
- ■ 2 Issues: Death, 1 CEF Issue (CHC)
- ■ 2 Issues: Death, 1 CEF Issue (HCC)
- ■ 2 Issues: Death, 1 CEF Issue (VHD)
- ■ 6 Issues: Death, 5 CEF Issues (HCC, CHC, VHD, CNSH, CVD)
- ■ 6 Issues: Death, 5 COMP Issues (AD, HT, J, R, BD)
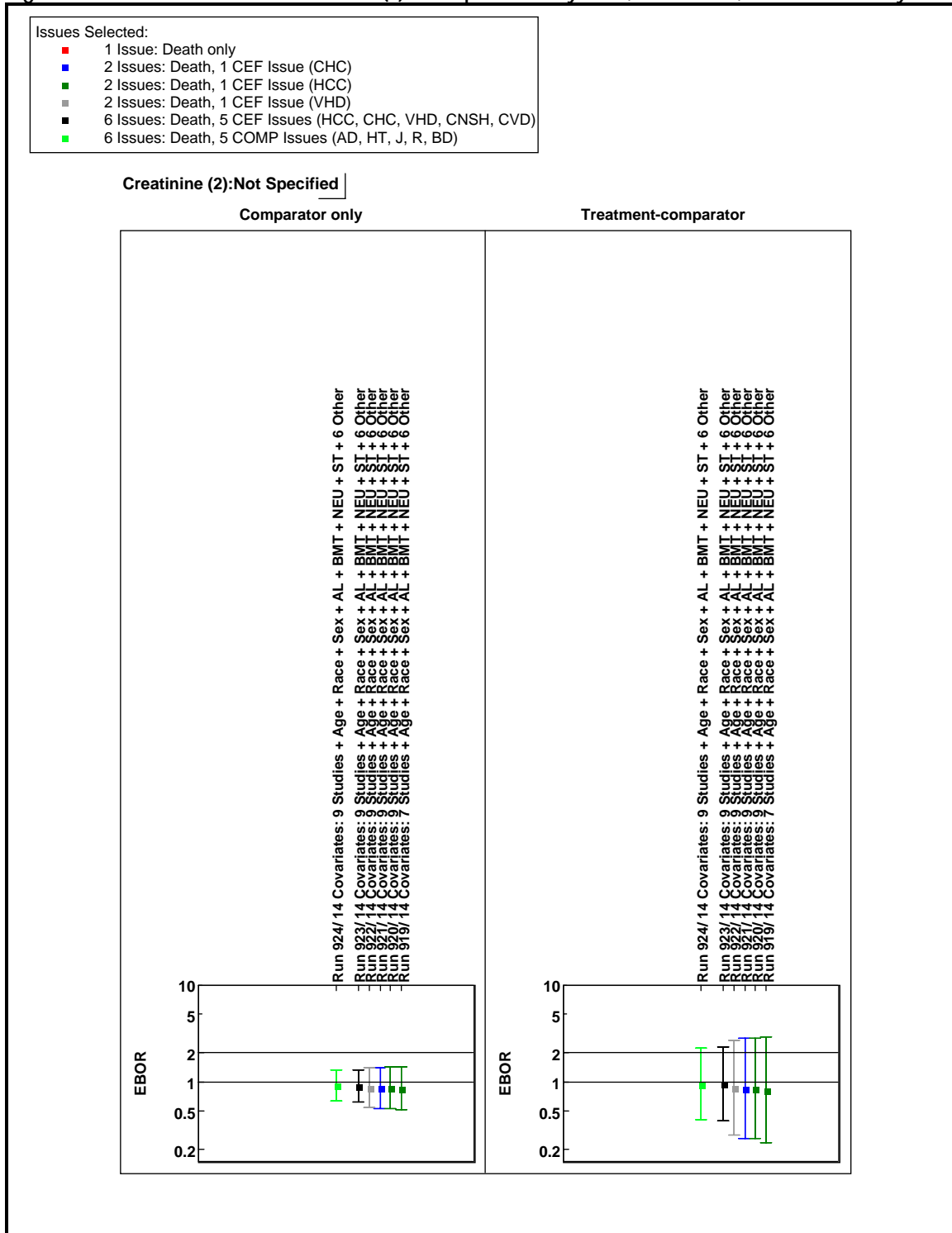
Figure 85: EBOR values for "Neutropenia (3):<=100" by runs, covariates, and issues analyzed
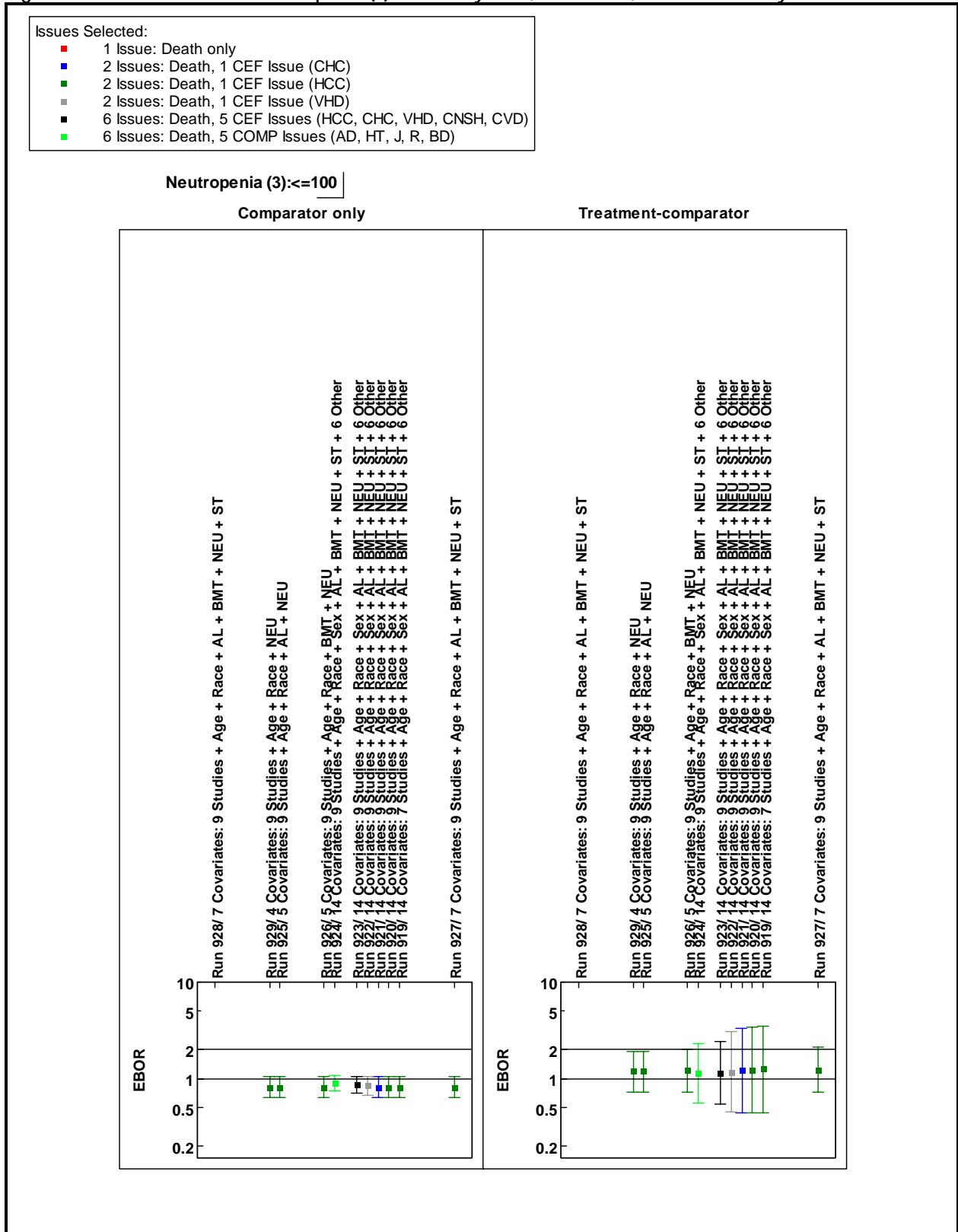
Figure 86: EBOR values for "Neutropenia (3):<=500" by runs, covariates, and issues analyzed
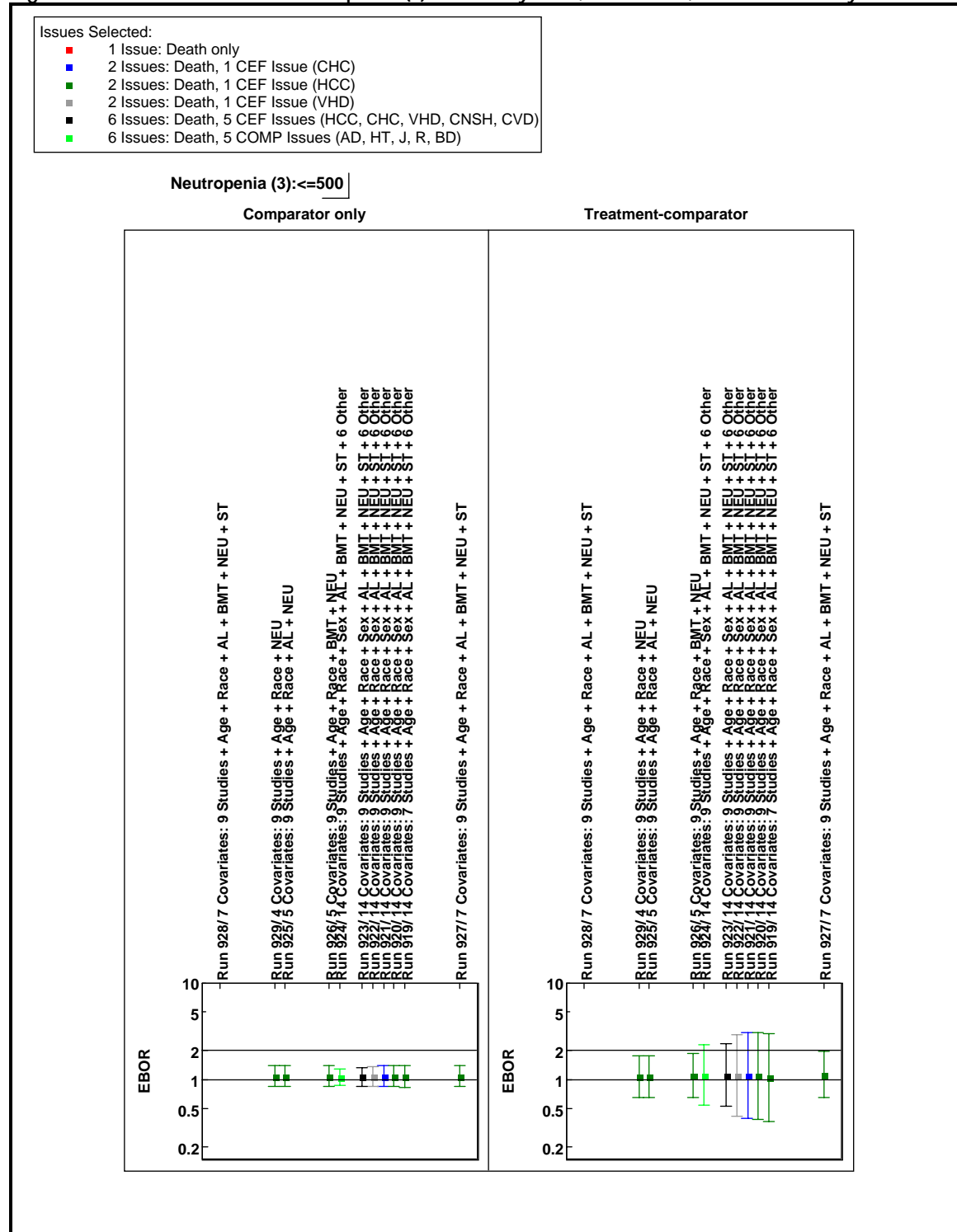
Figure 87: EBOR values for "Neutropenia (3):>500" by runs, covariates, and issues analyzed
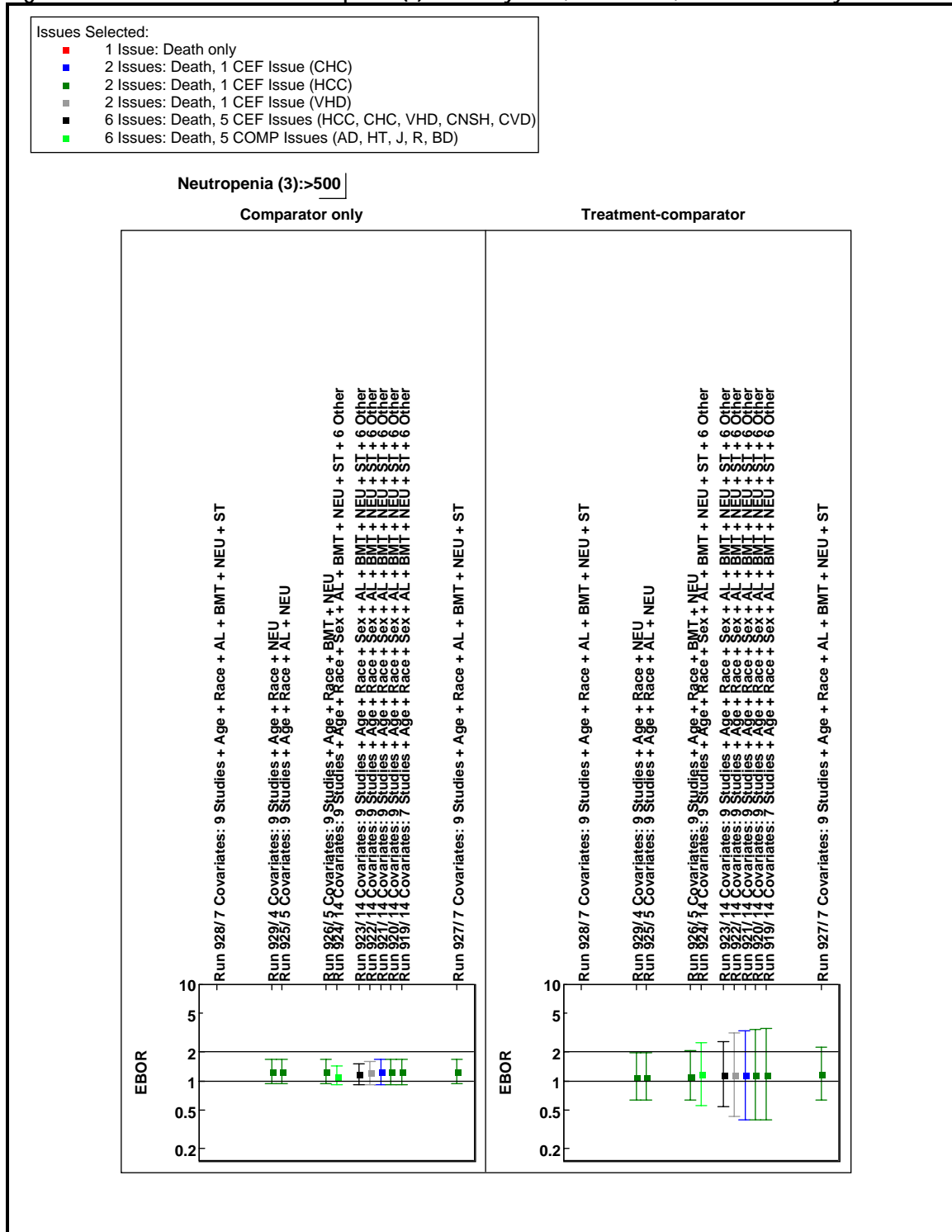
Figure 88: EBOR values for "Neutropenia (3):Not Specified" by runs, covariates, and issues analyzed

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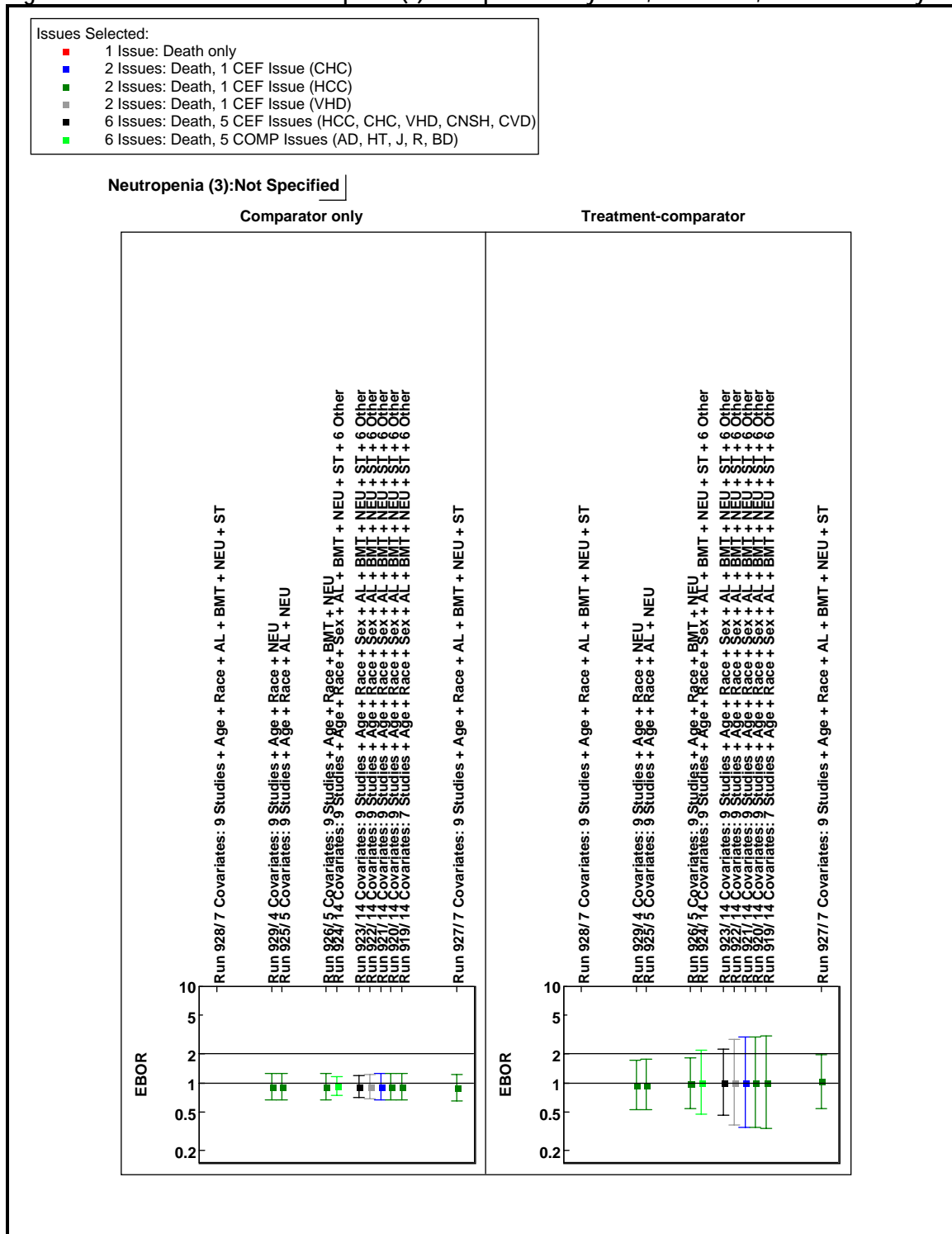
4.15. *Unadjusted OR Values Across 25 MBLR Runs*

Figure 89: Overall OR values by runs and covariates analyzed
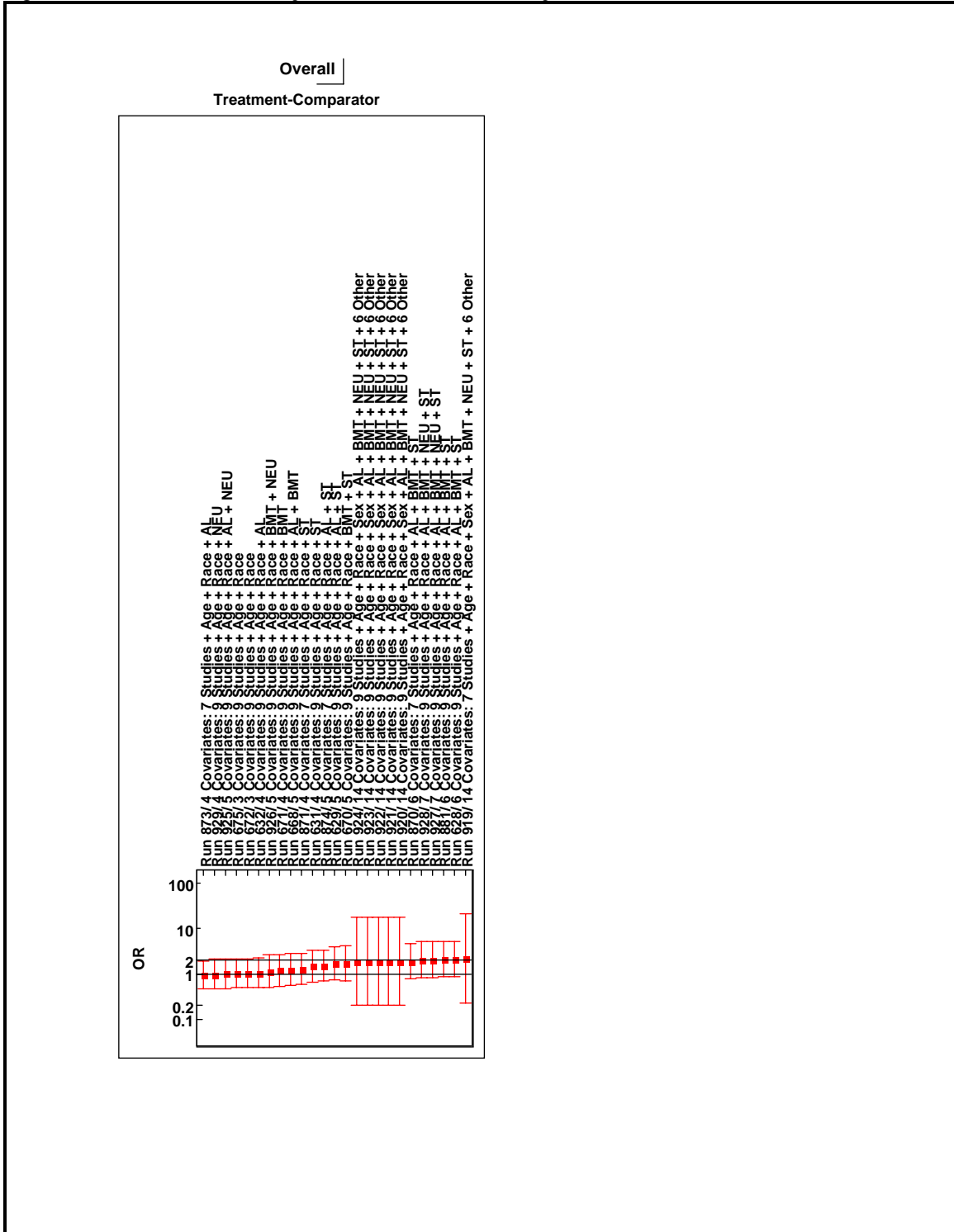
Figure 90: OR values for "Sex:F" by runs and covariates analyzed
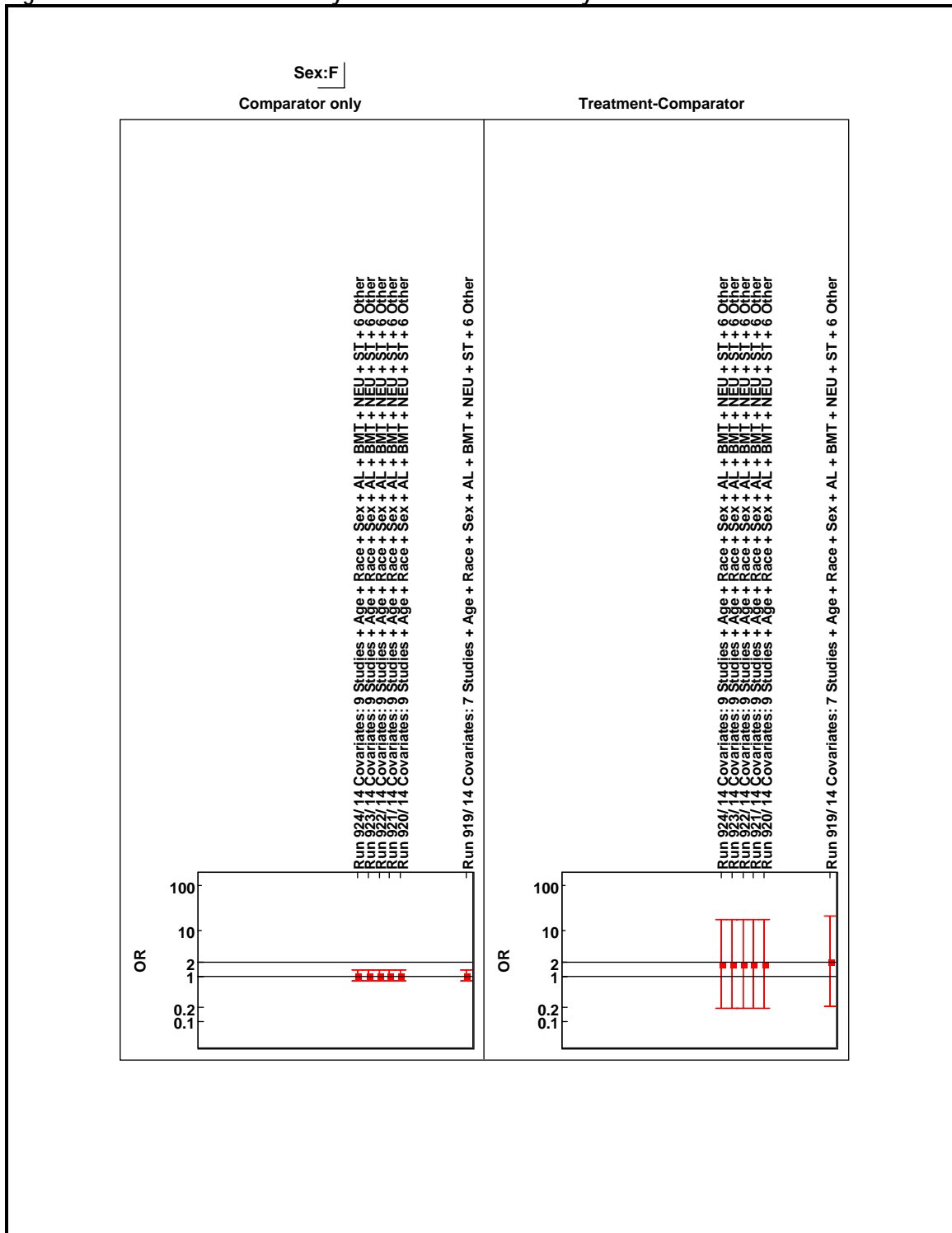
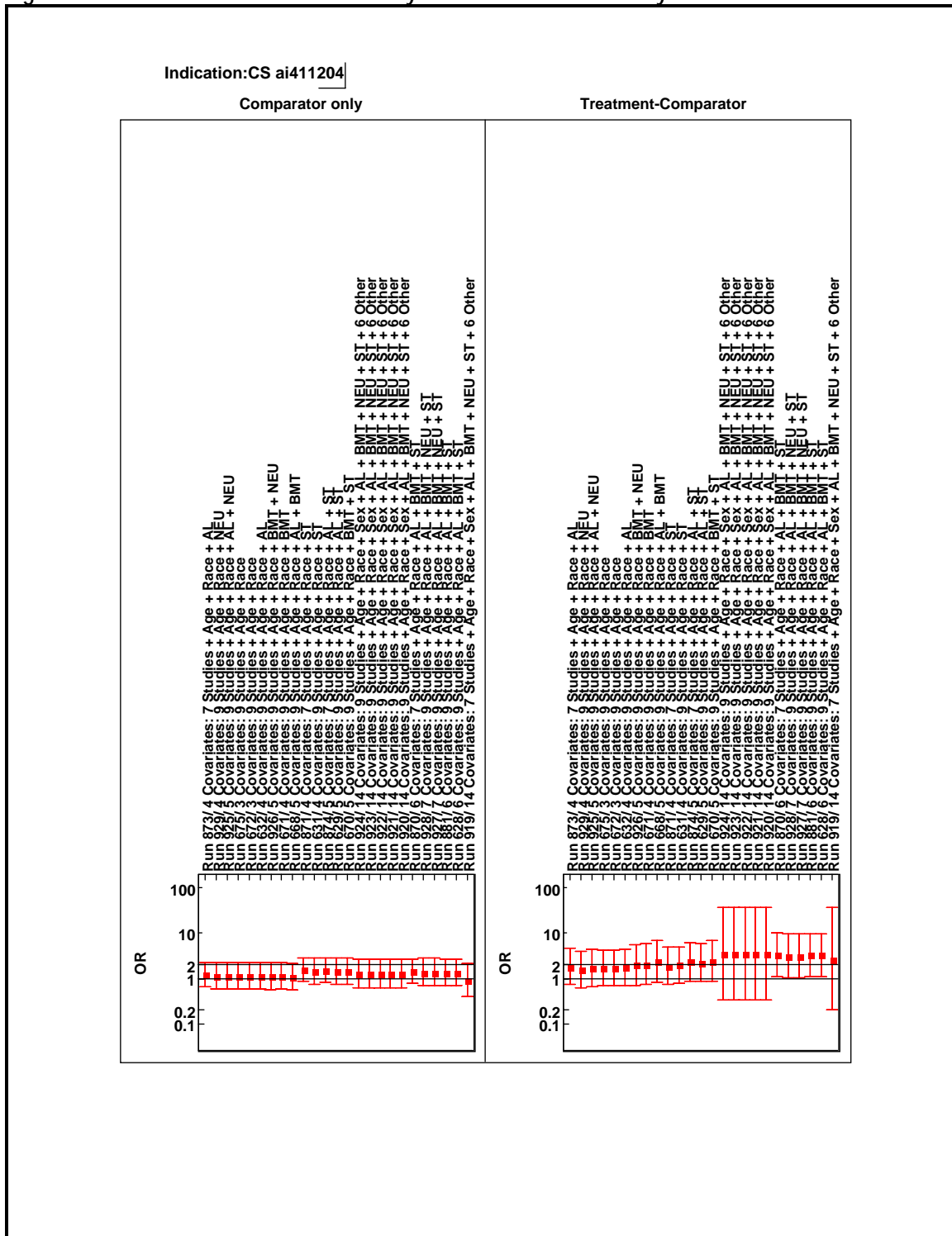Figure 91: OR values for "Sex:M" by runs and covariates analyzed
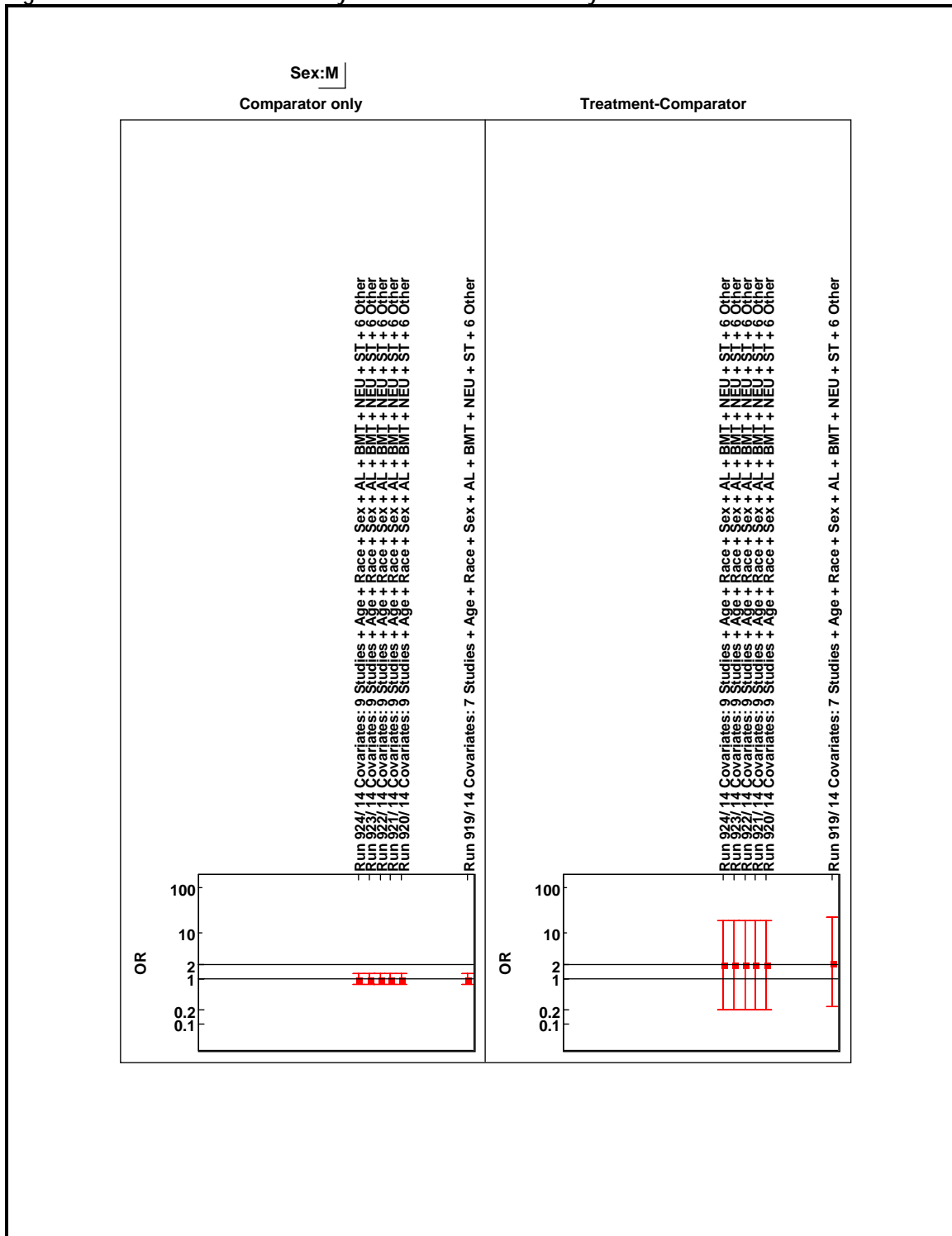
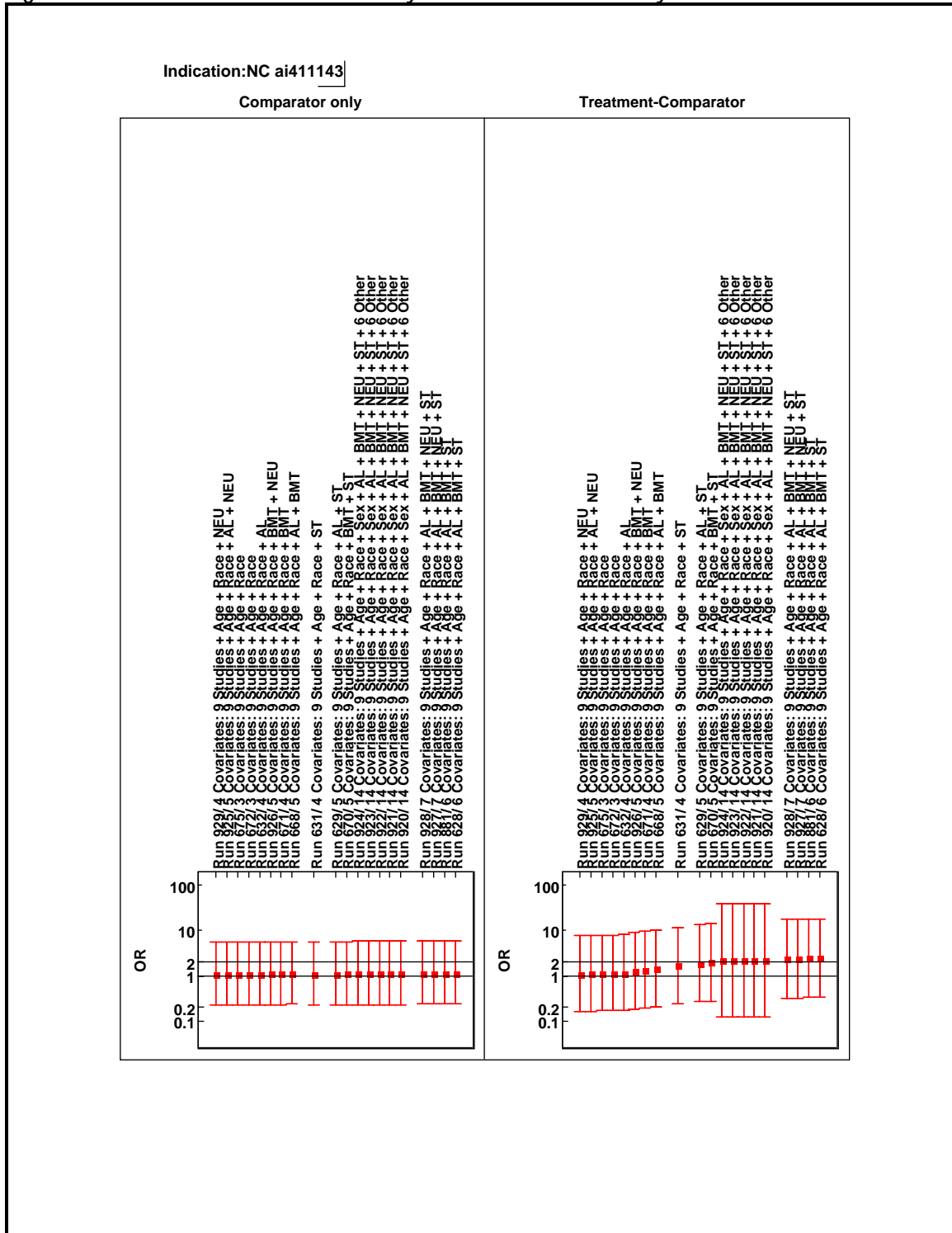Figure 92: OR values for "Race:Other" by runs and covariates analyzed
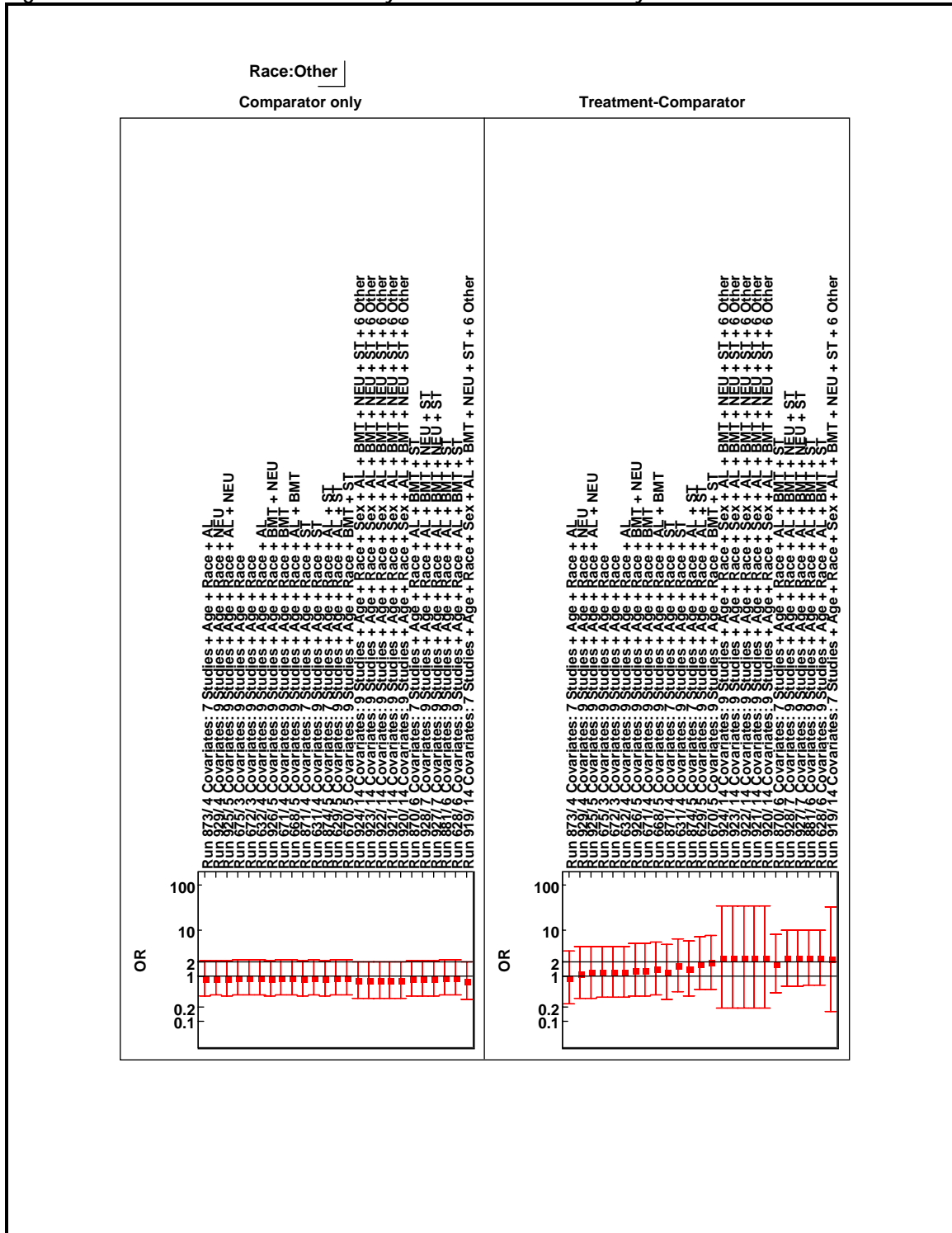
Figure 93: OR values for "Race:Black" by runs and covariates analyzed
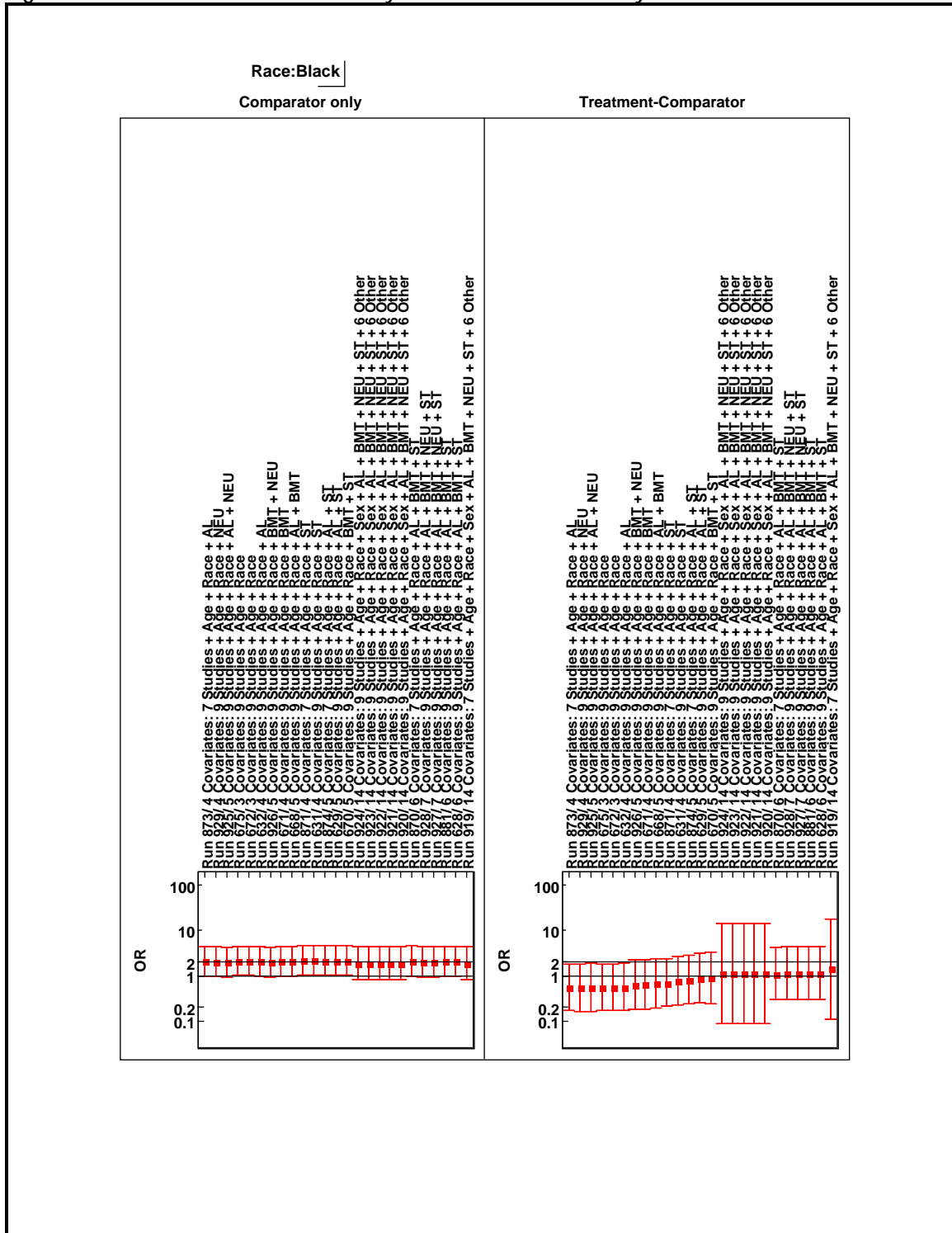
Figure 94: OR values for "Race:White" by runs and covariates analyzed

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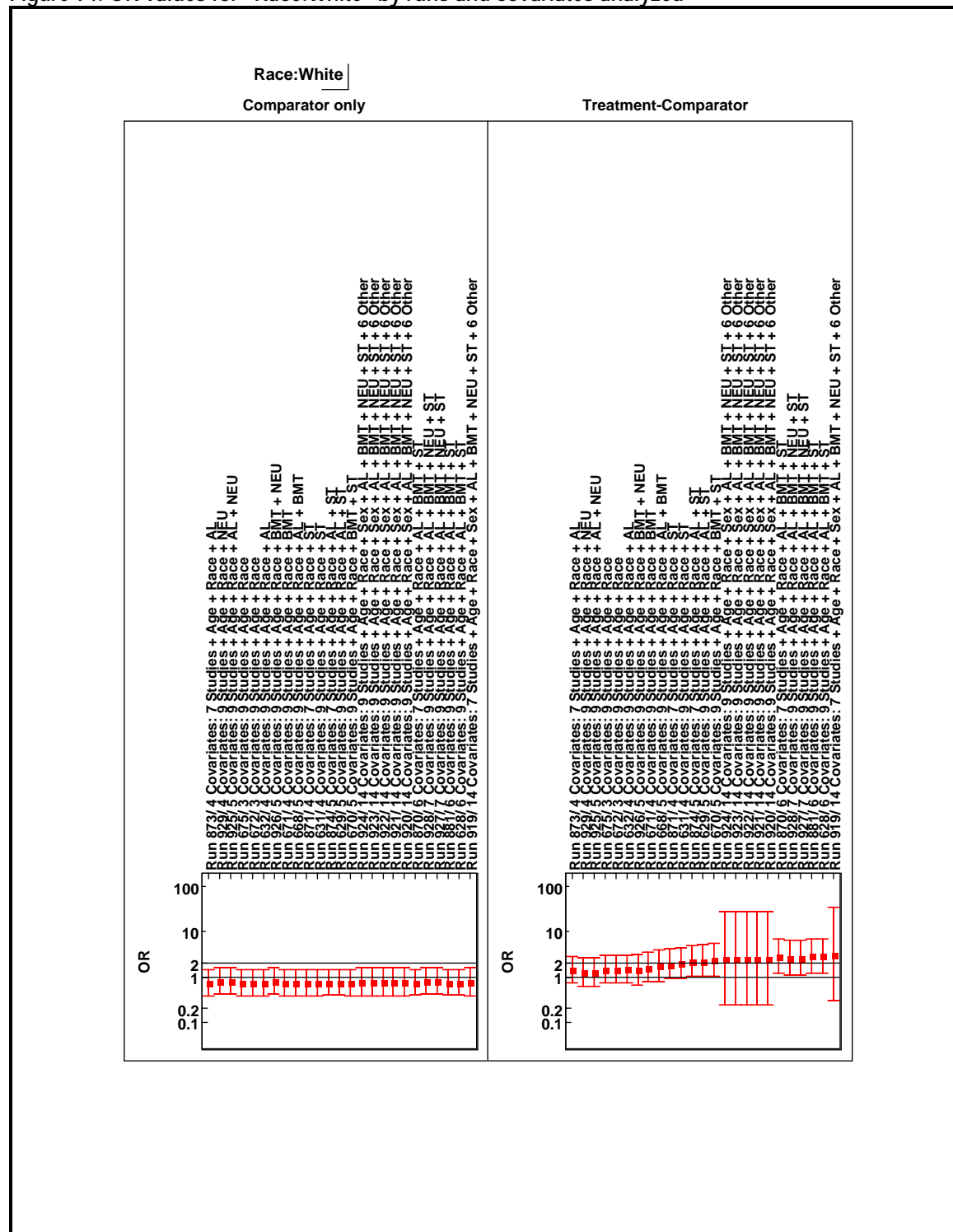
Figure 95: OR values for "Race:Other or Not Specified" by runs and covariates analyzed
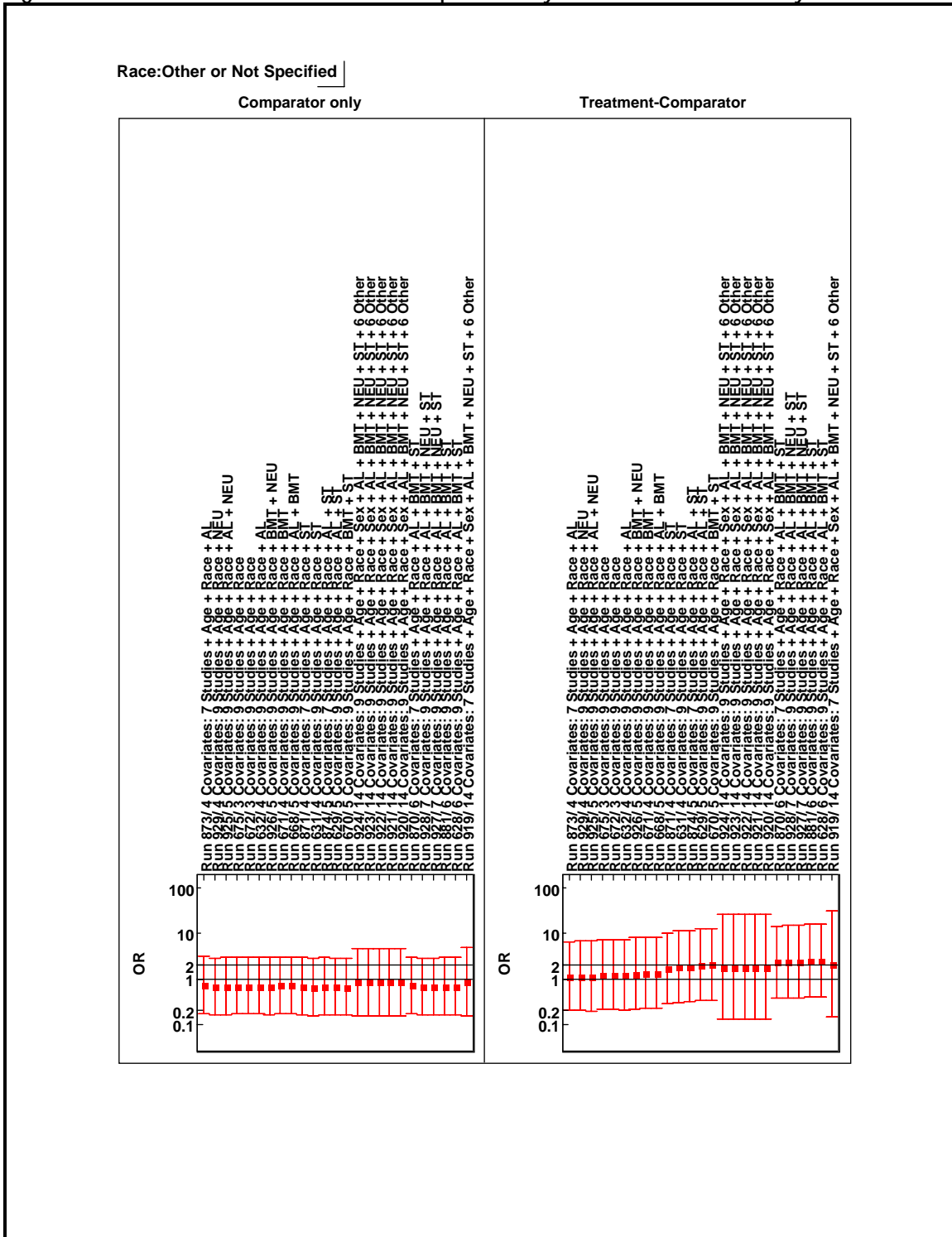
Figure 96: OR values for "CS ai411118" by runs and covariates analyzed
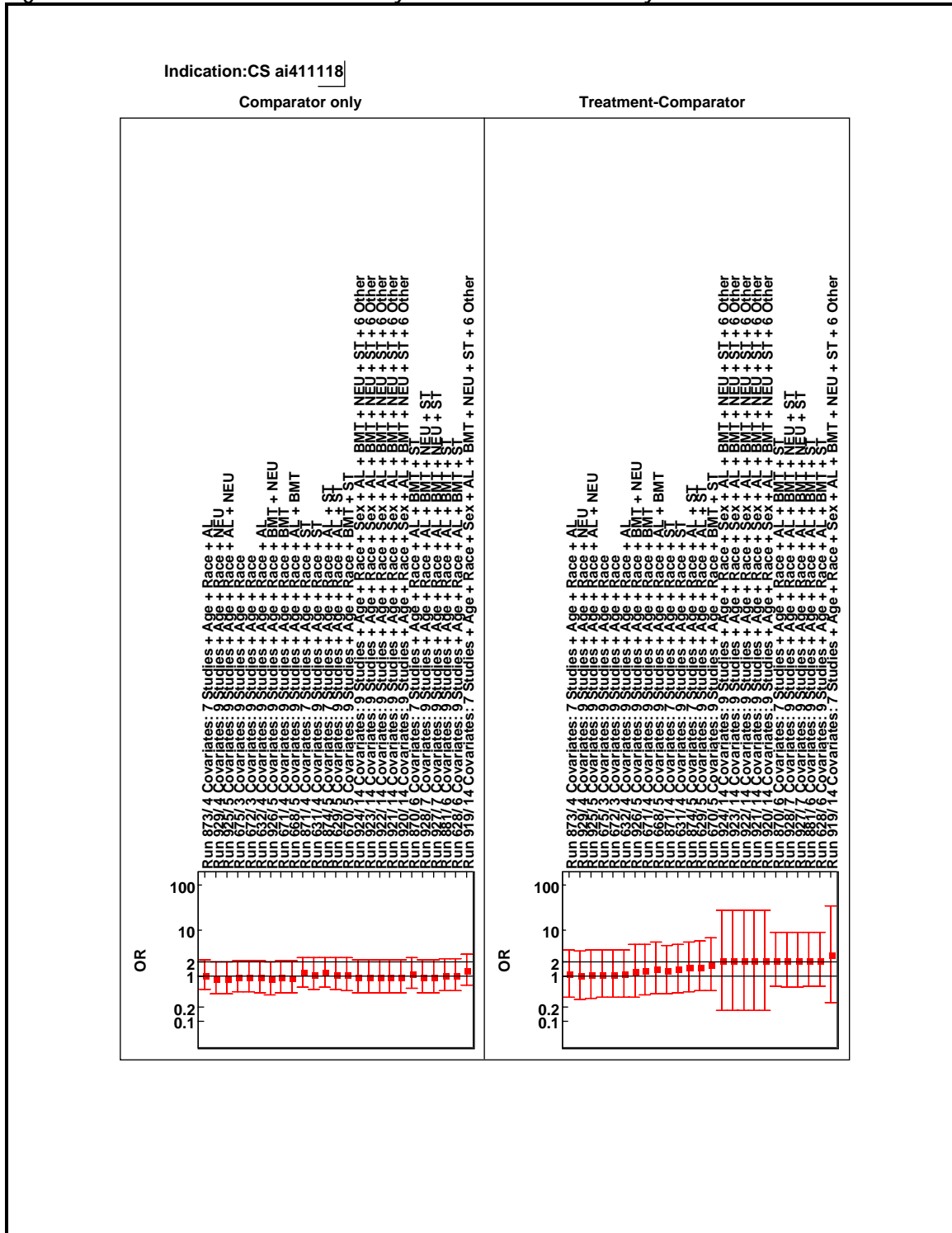
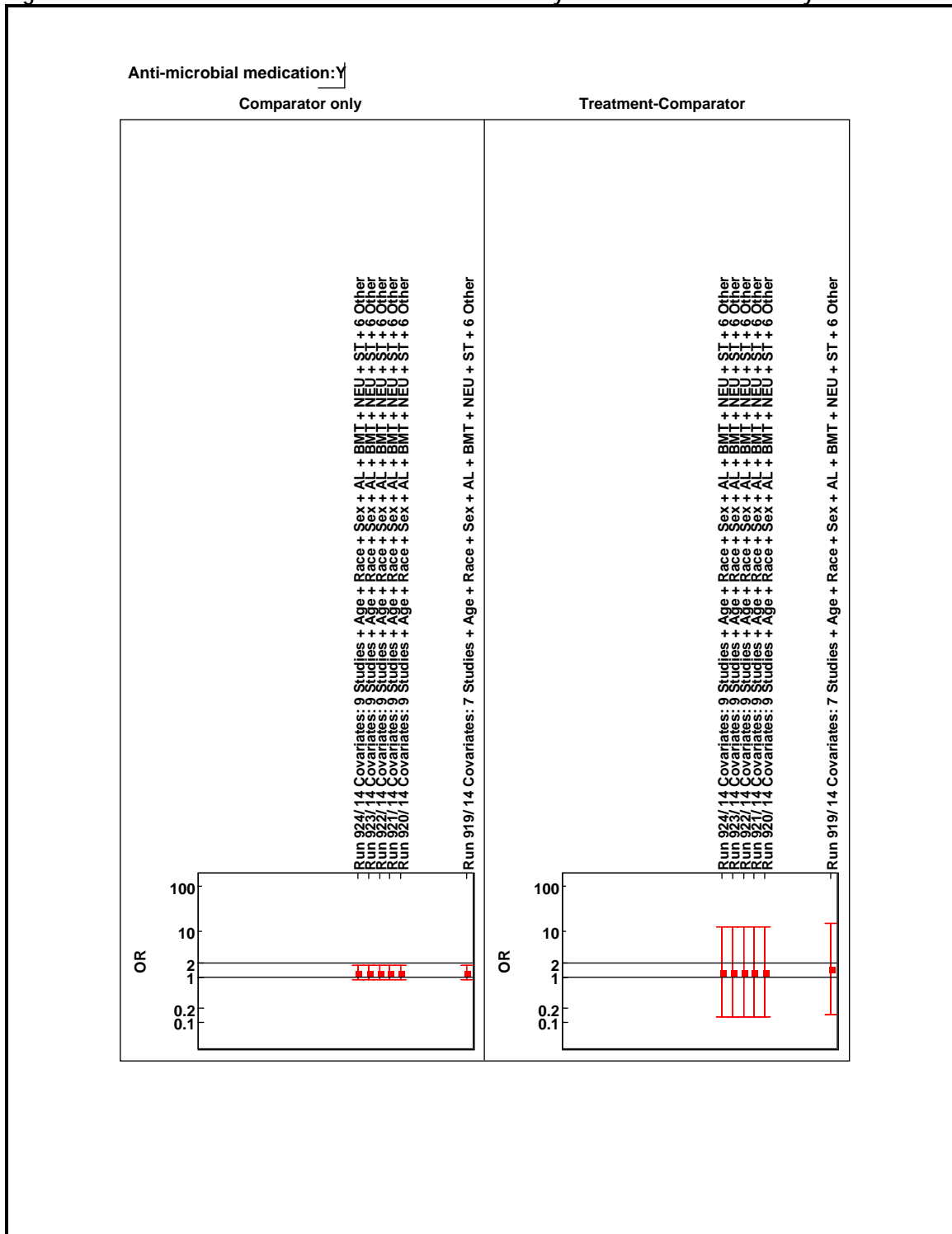Figure 97: OR values for "CS ai411131" by runs and covariates analyzed
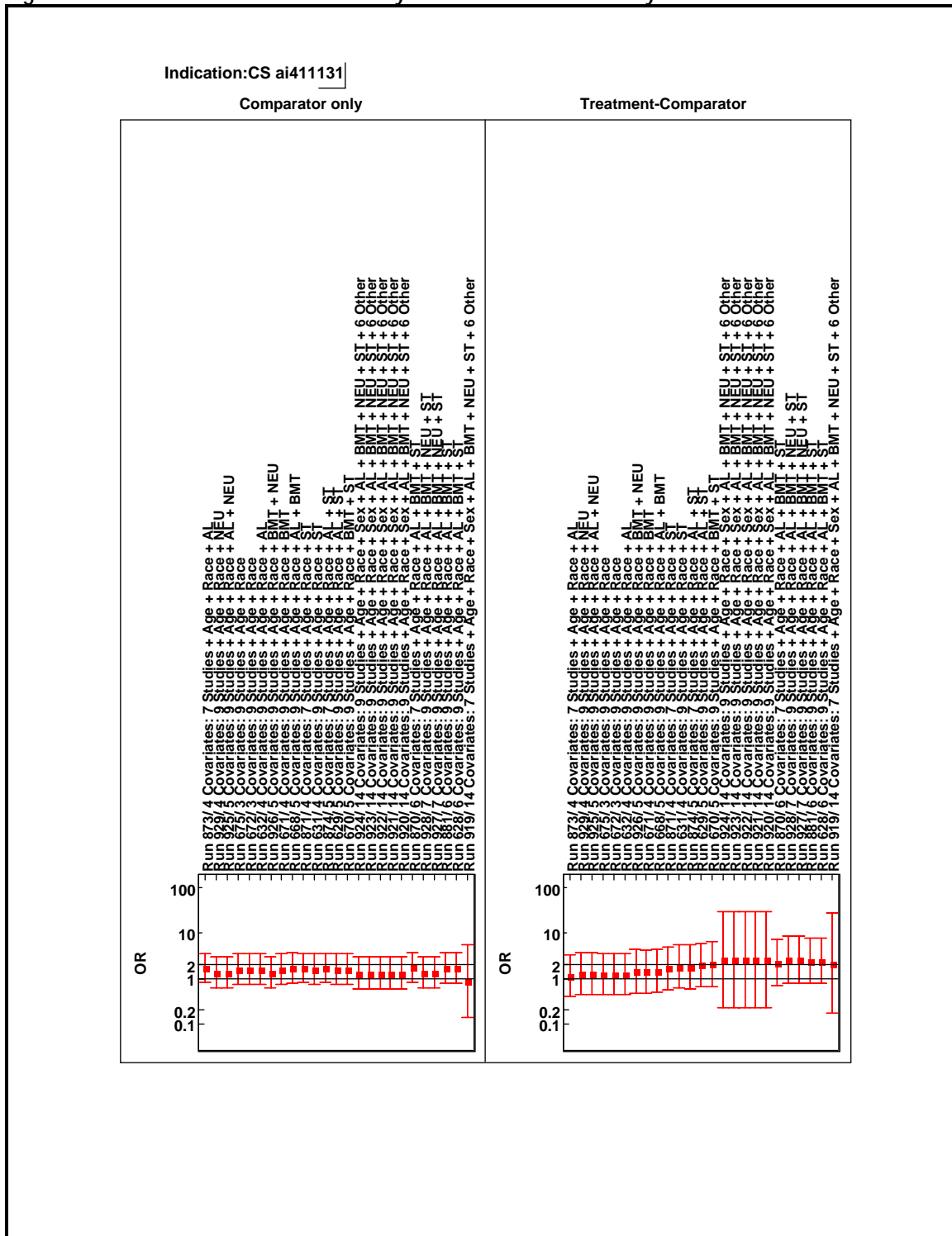
Figure 98: OR values for "CS ai411186" by runs and covariates analyzed
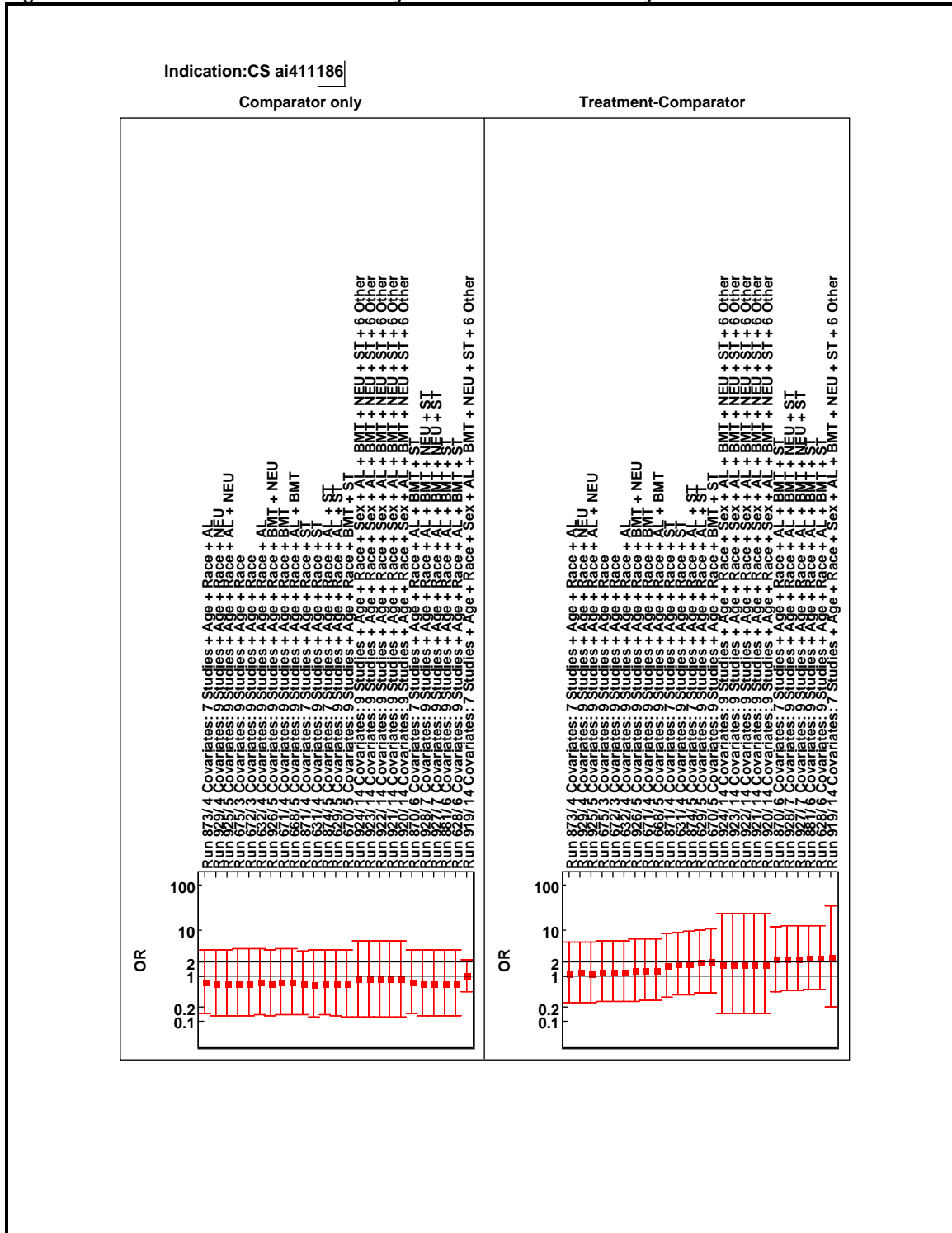
Figure 99: OR values for "CS ai411137" by runs and covariates analyzed
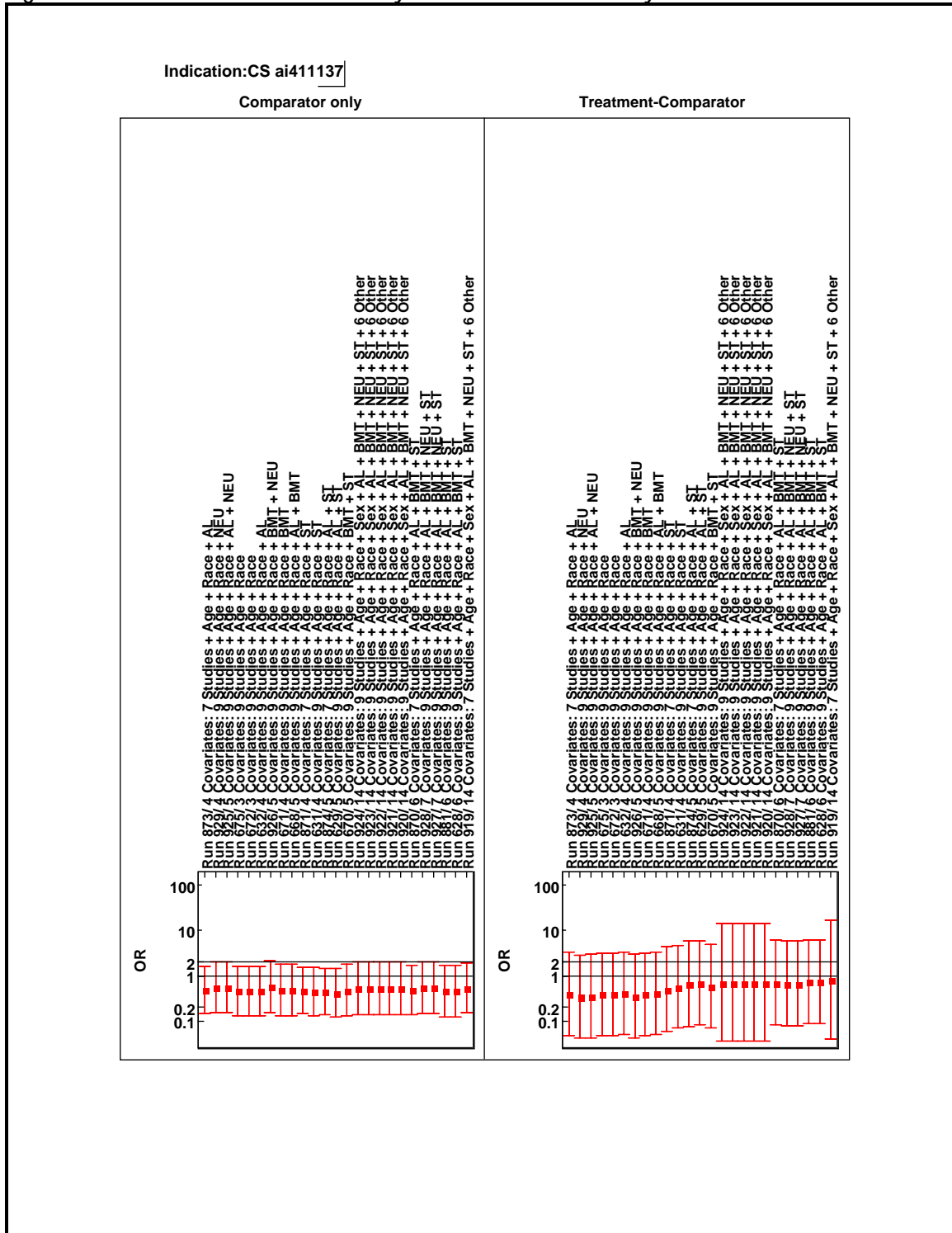
Figure 100: OR values for "CS ai411189" by runs and covariates analyzed
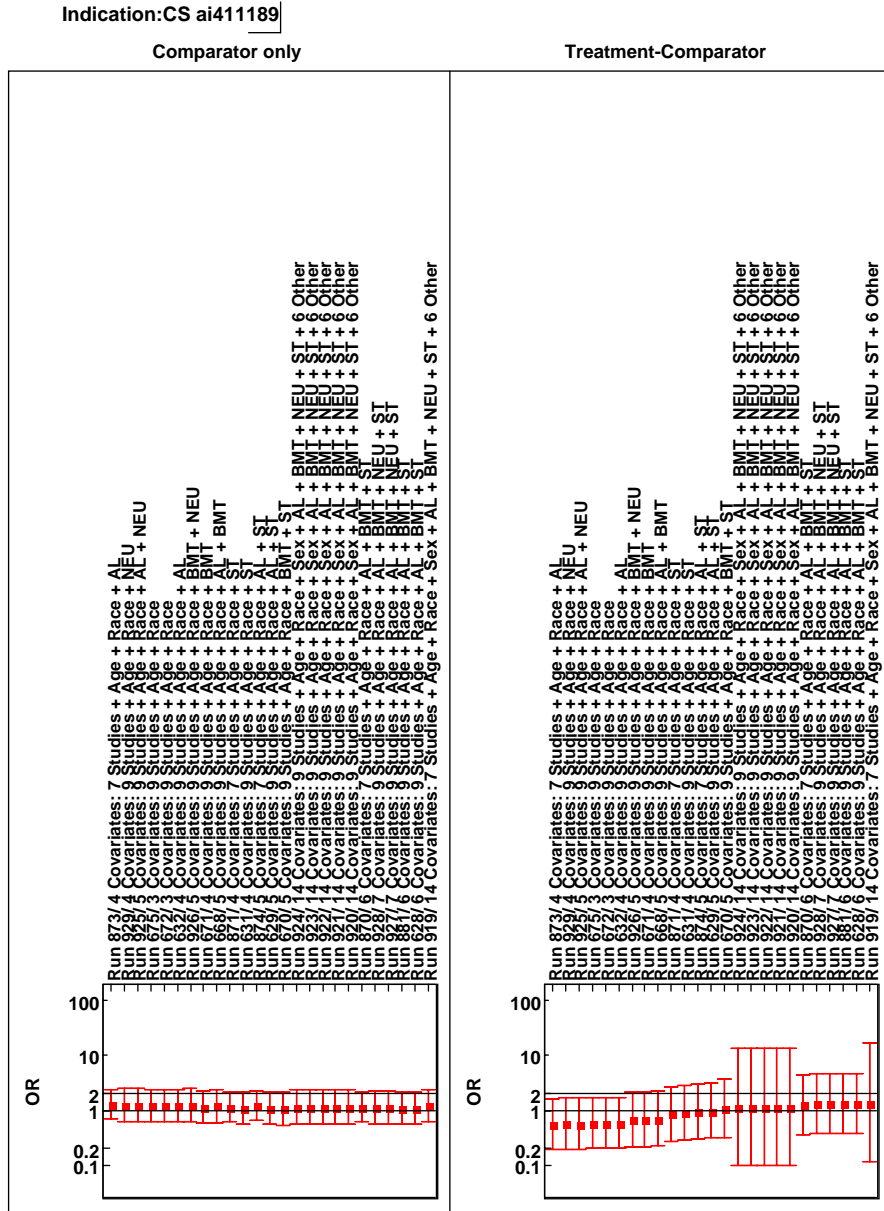
Figure 101: OR values for "CS ai411198" by runs and covariates analyzed
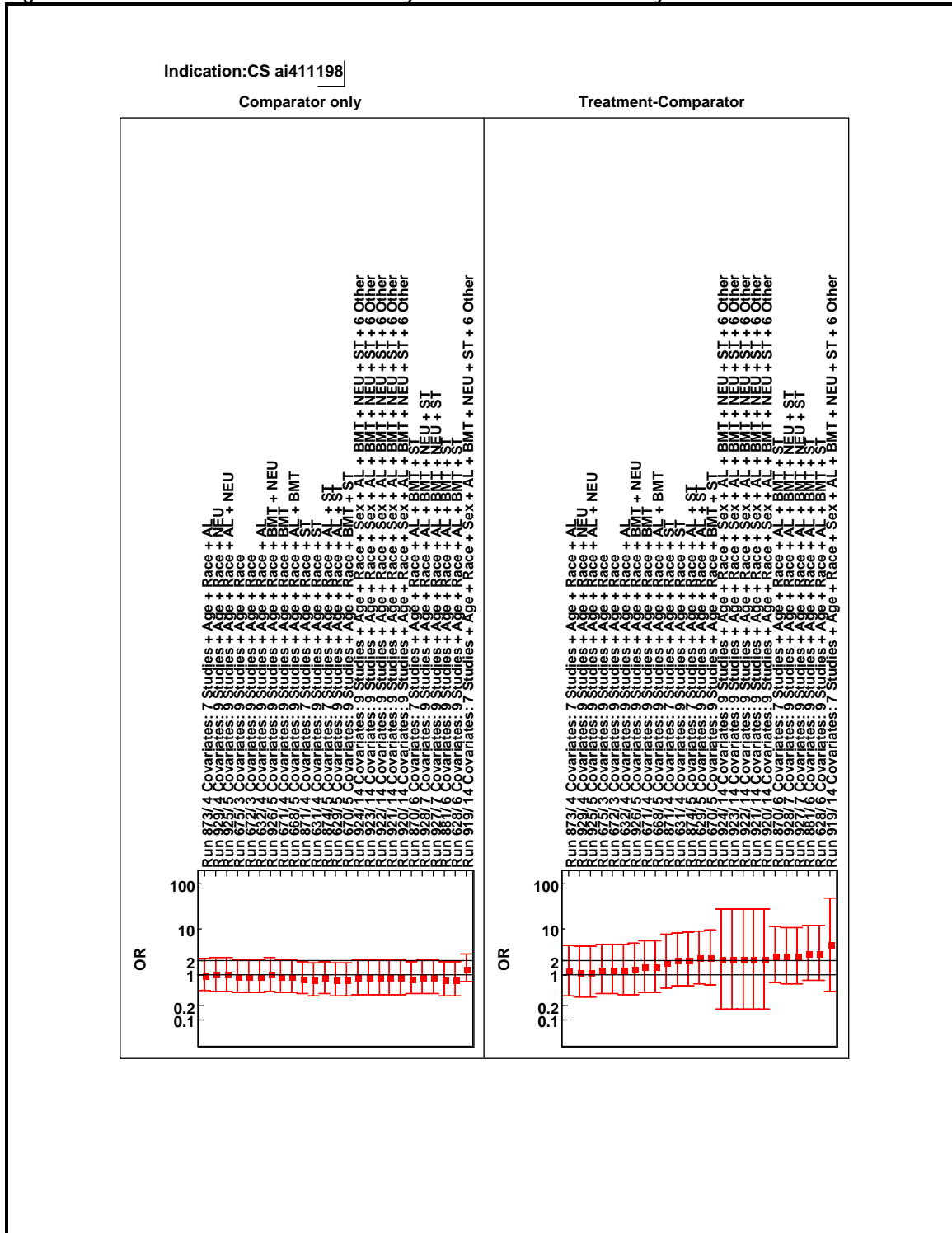
Figure 102: OR values for "CS ai411204" by runs and covariates analyzed

Figure 103: OR values for "NC ai411143" by runs and covariates analyzed

Figure 104: OR values for "NC ai411158" by runs and covariates analyzed

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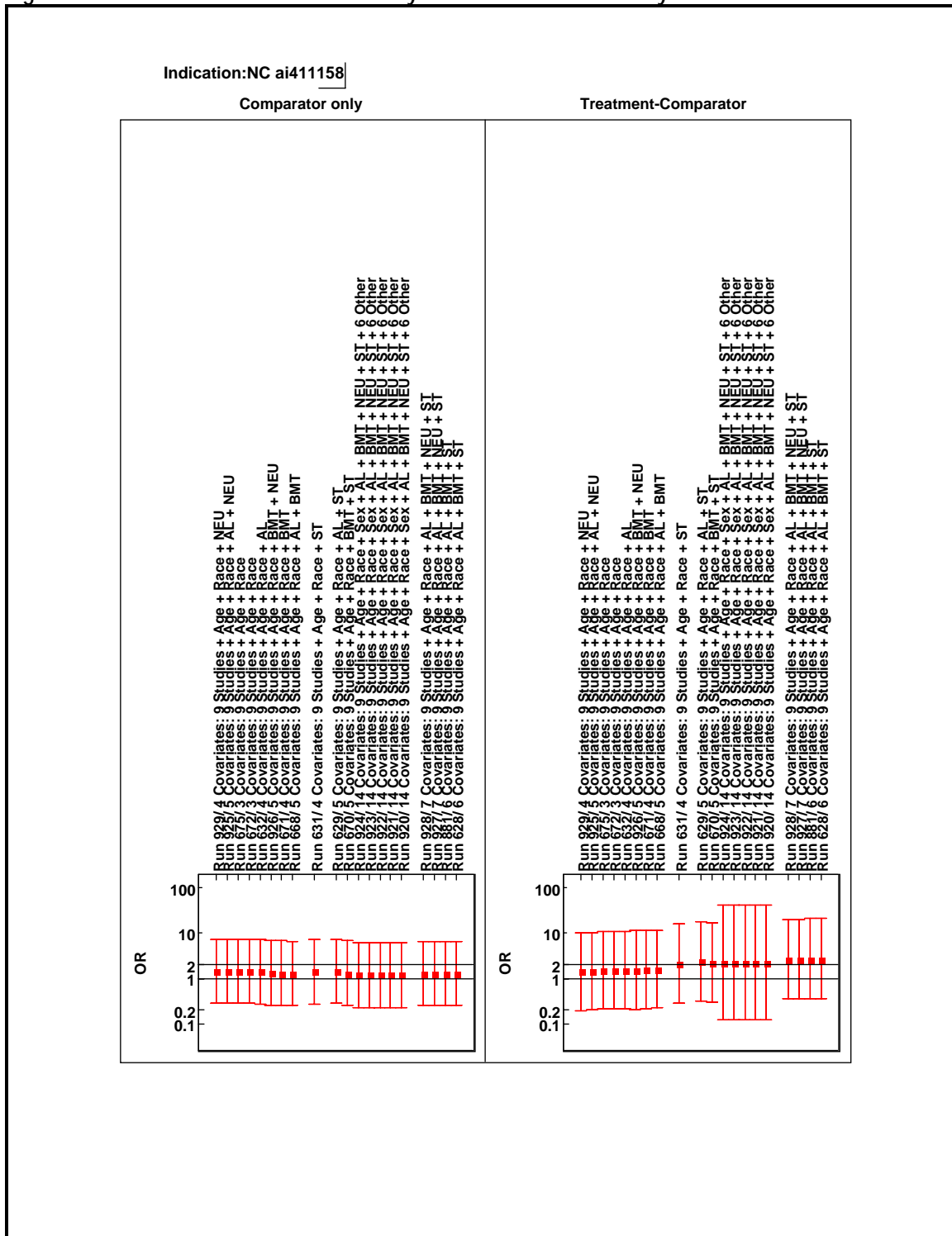
Figure 105: OR values for "Anti-microbial medication:Y" by runs and covariates analyzed

Figure 106: OR values for "Anti-microbial medication:N" by runs and covariates analyzed
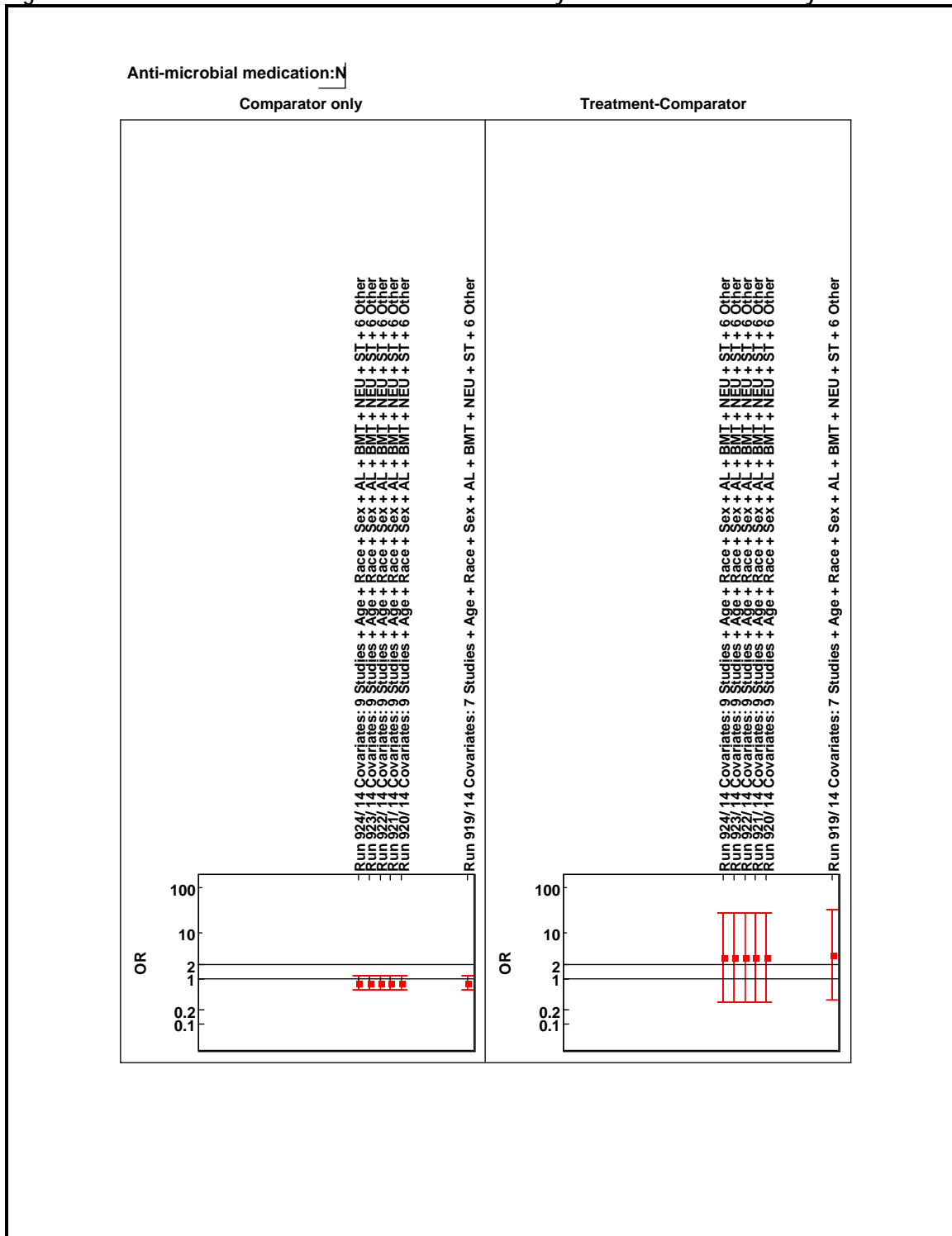
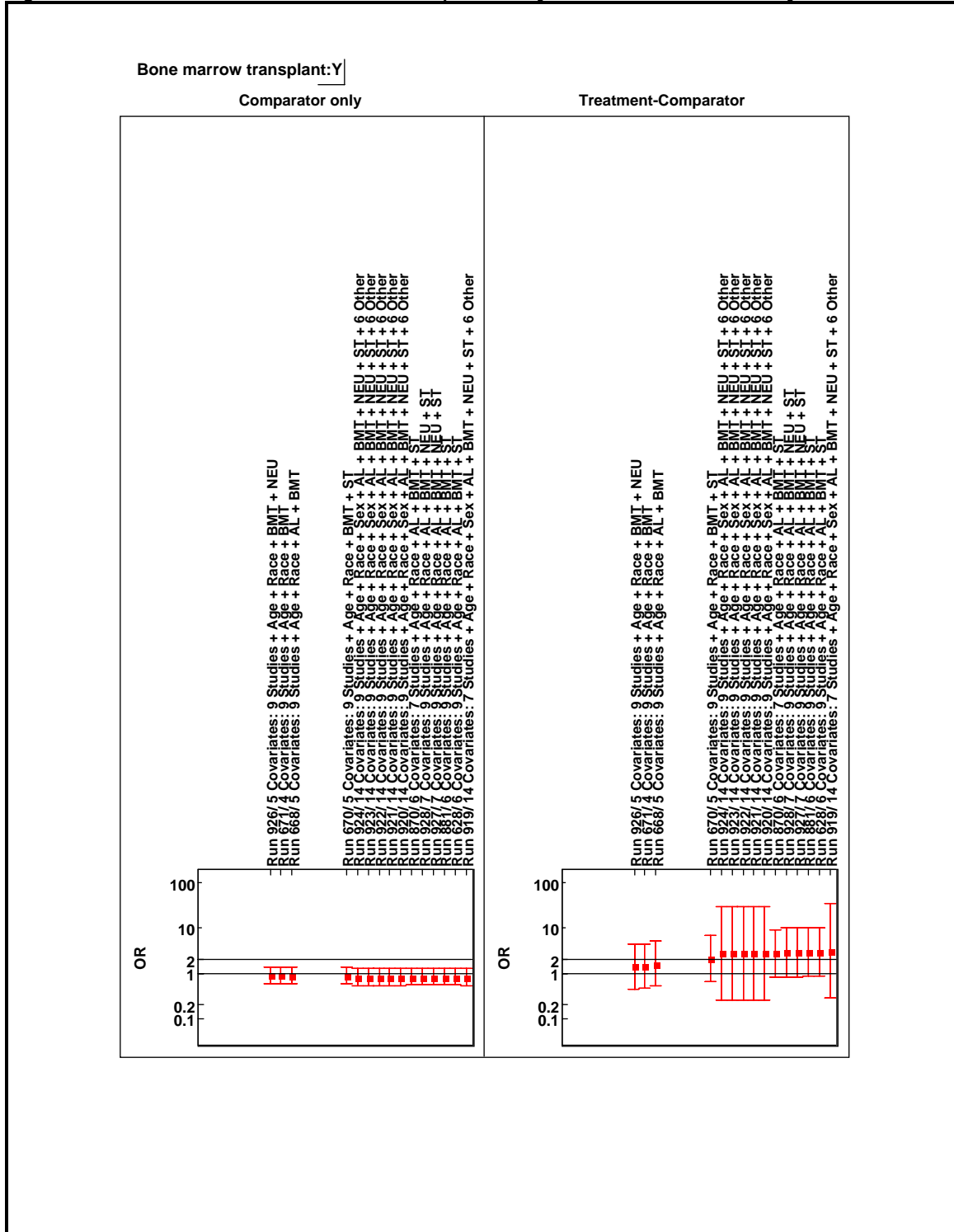Figure 107: OR values for "Bone marrow transplant:Y" by runs and covariates analyzed

Figure 108: OR values for "Bone marrow transplant:N" by runs and covariates analyzed
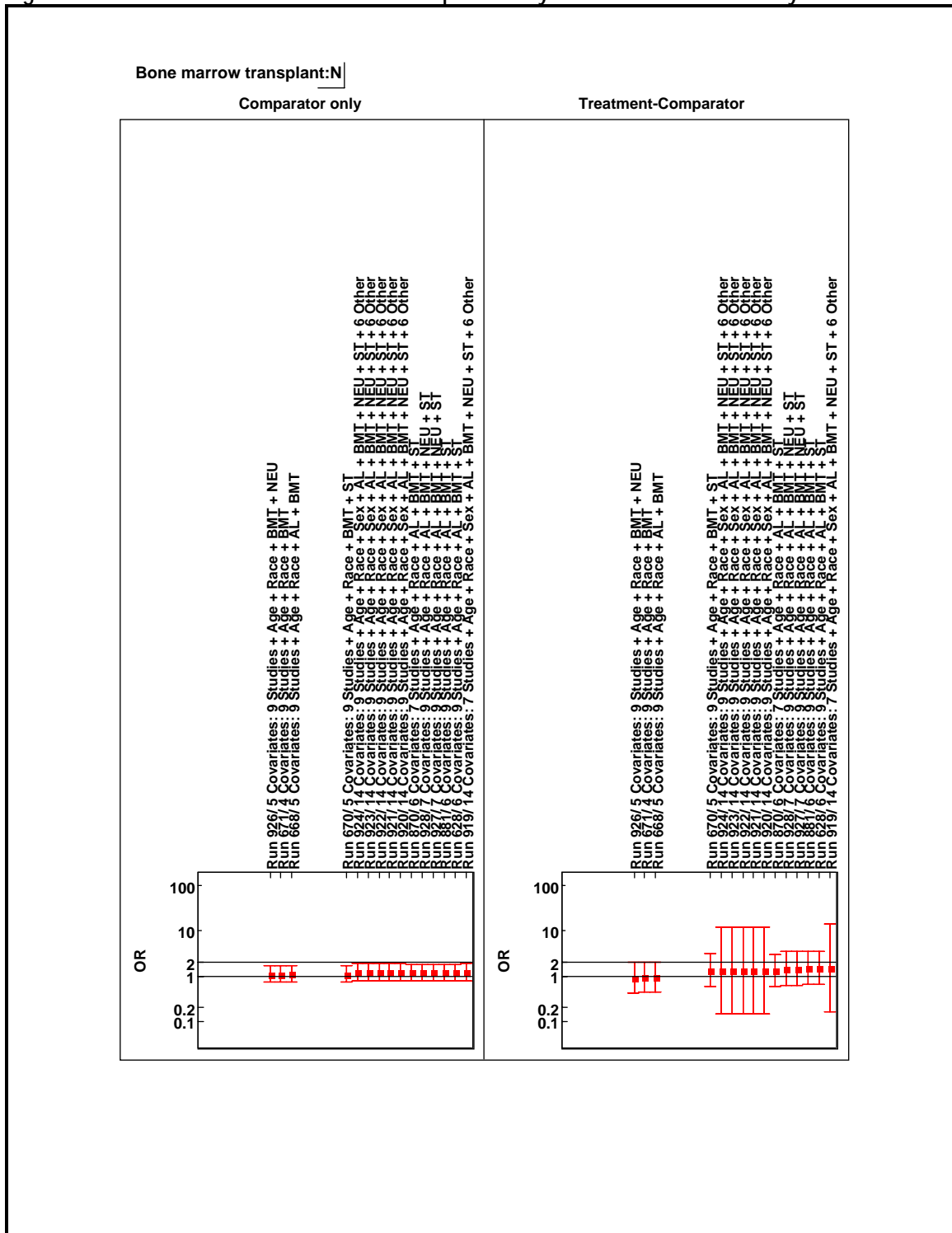
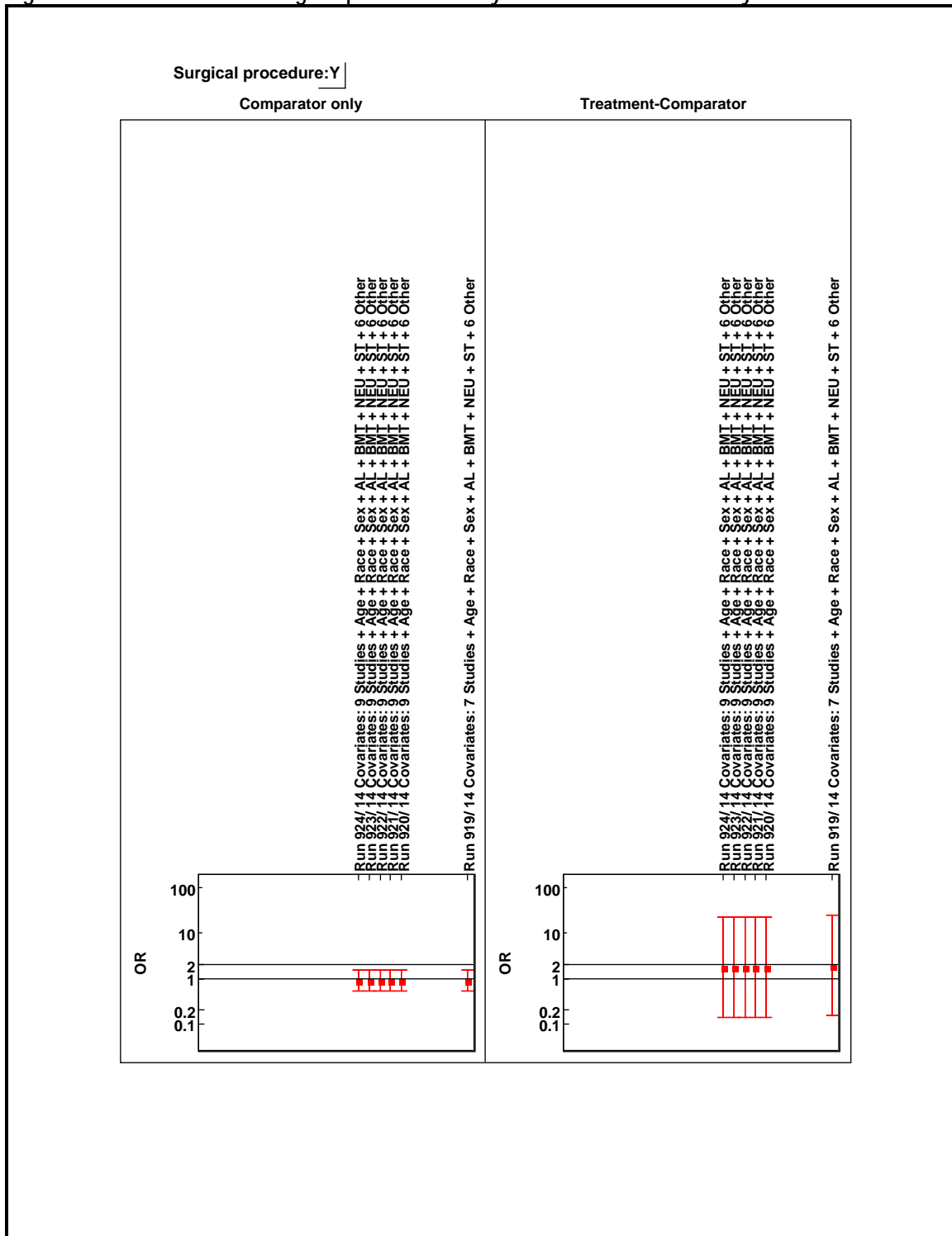Figure 109: OR values for "Surgical procedure:Y" by runs and covariates analyzed

Figure 110: OR values for "Surgical procedure:N" by runs and covariates analyzed
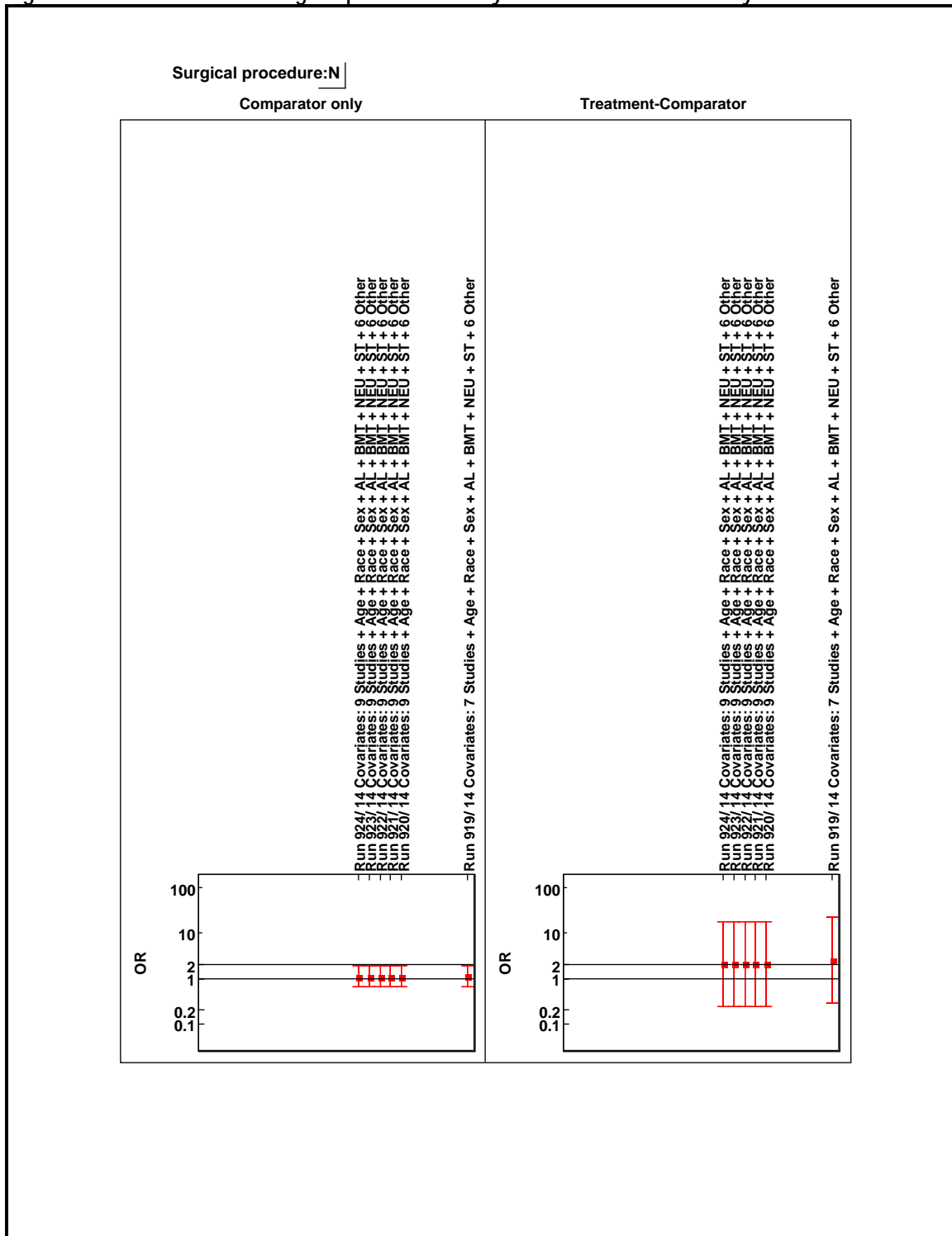
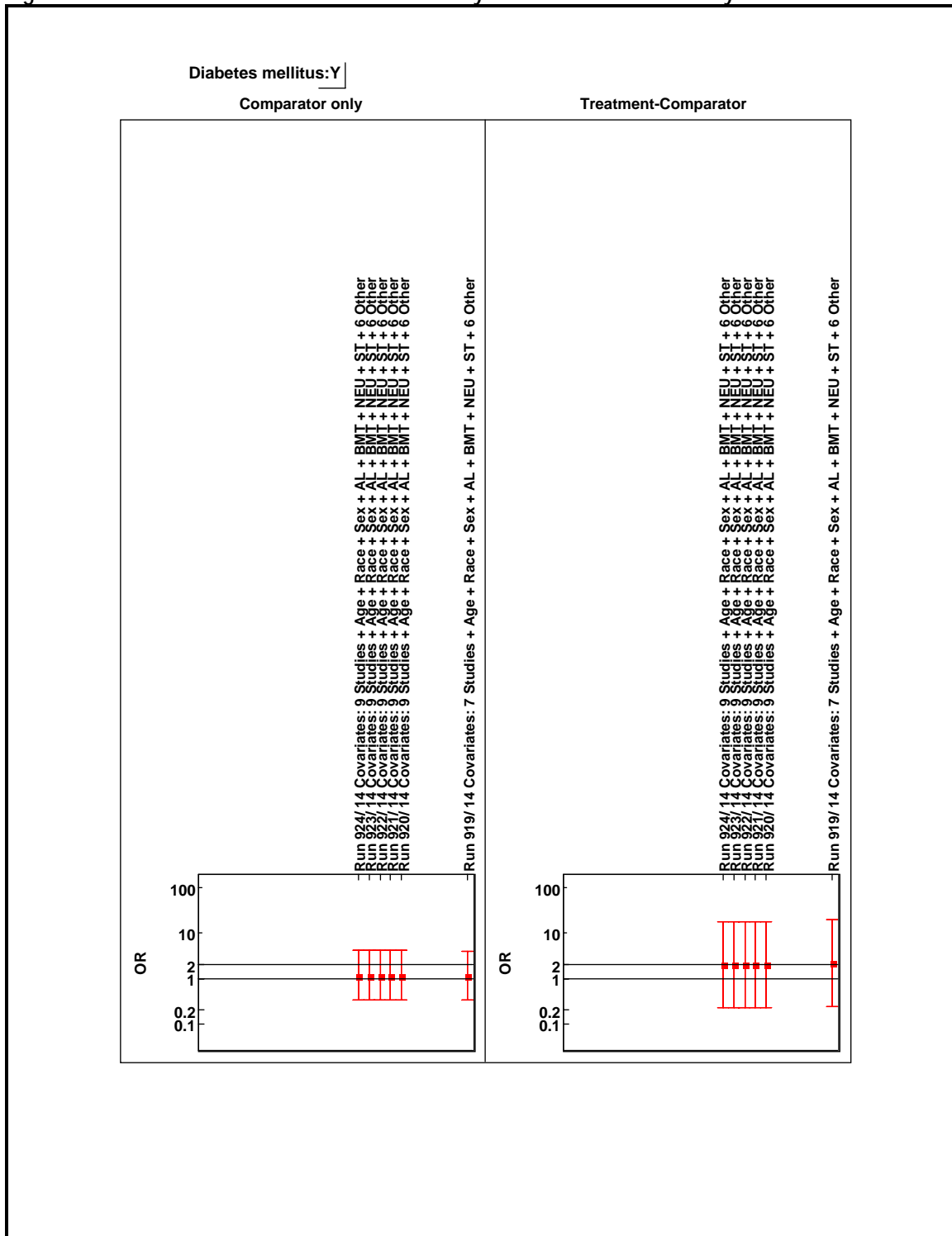Figure 111: OR values for "Diabetes mellitus:Y" by runs and covariates analyzed

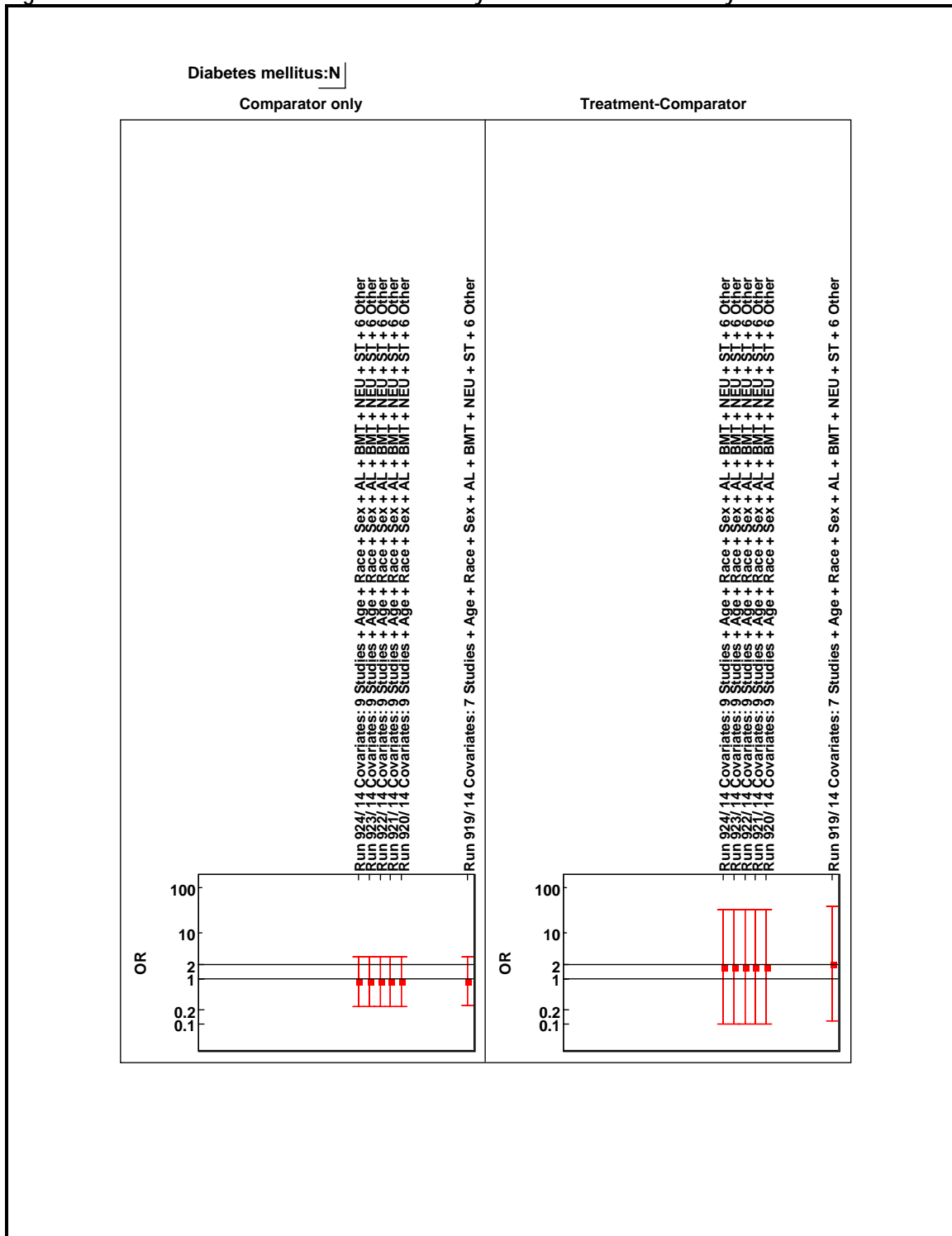Figure 112: OR values for "Diabetes mellitus:N" by runs and covariates analyzed

Figure 113: OR values for "Renal impairement:Y" by runs and covariates analyzed

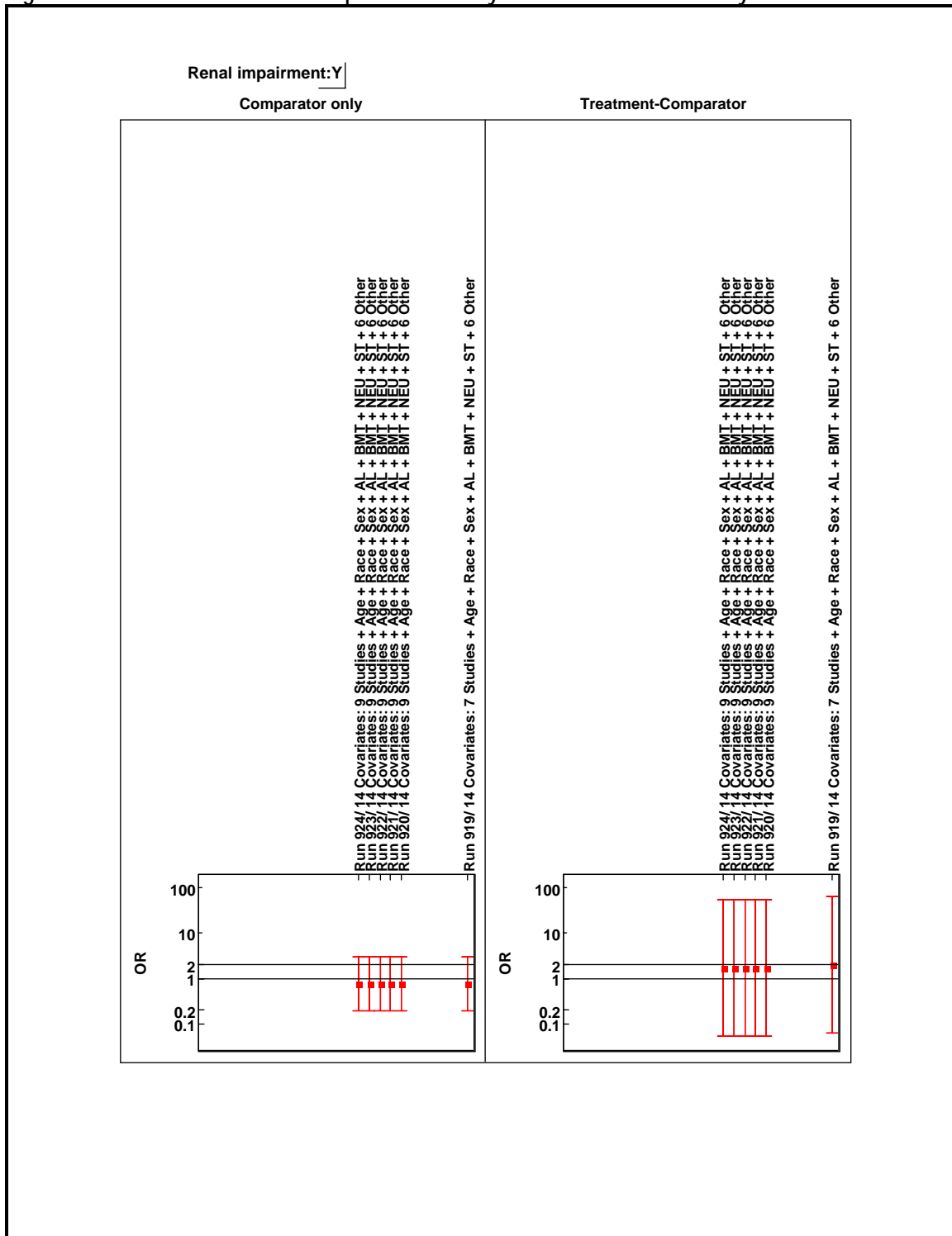Figure 114: OR values for "Renal impairement:N" by runs and covariates analyzed
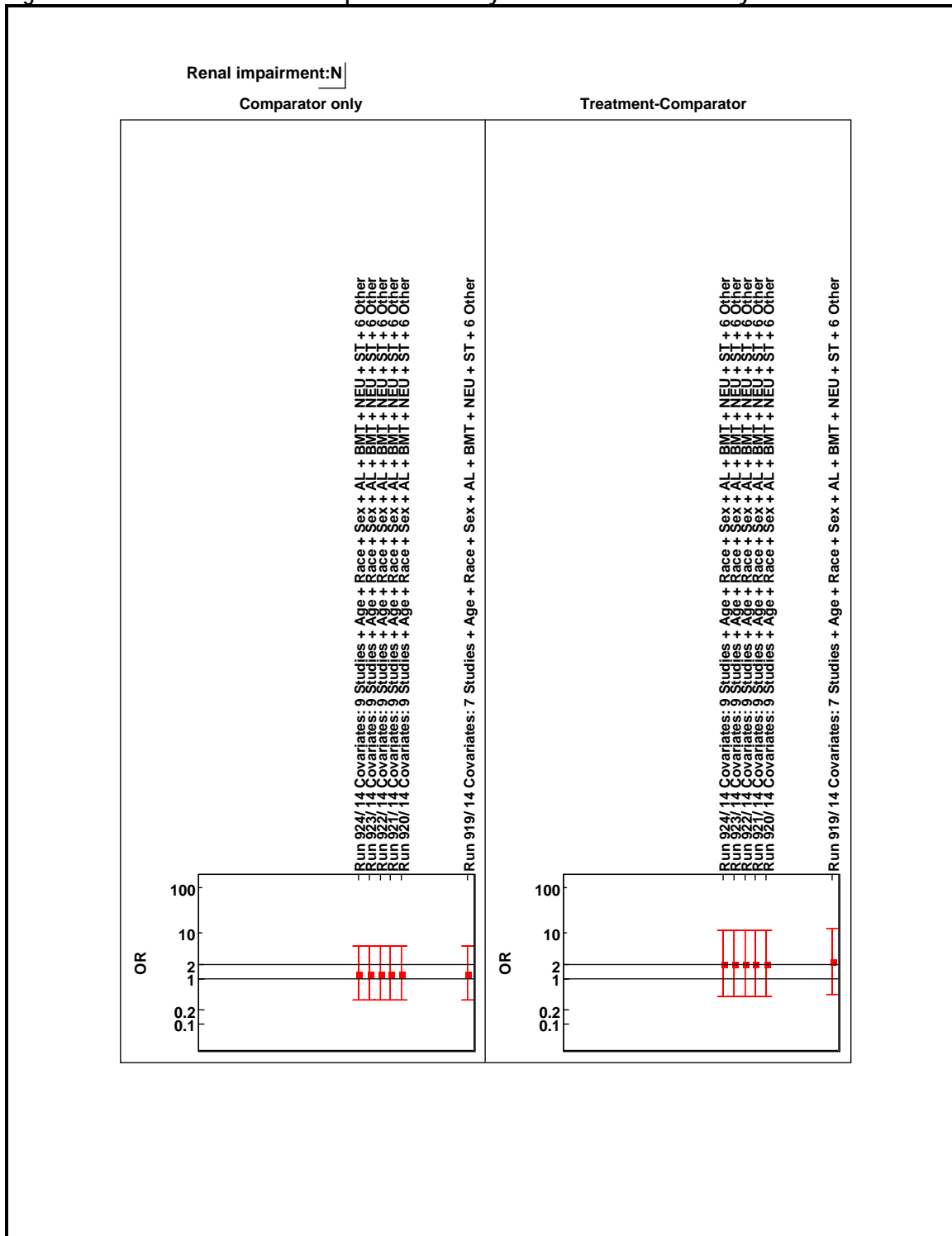
Figure 115: OR values for "Lymphoma/multiple myeloma:Y" by runs and covariates analyzed
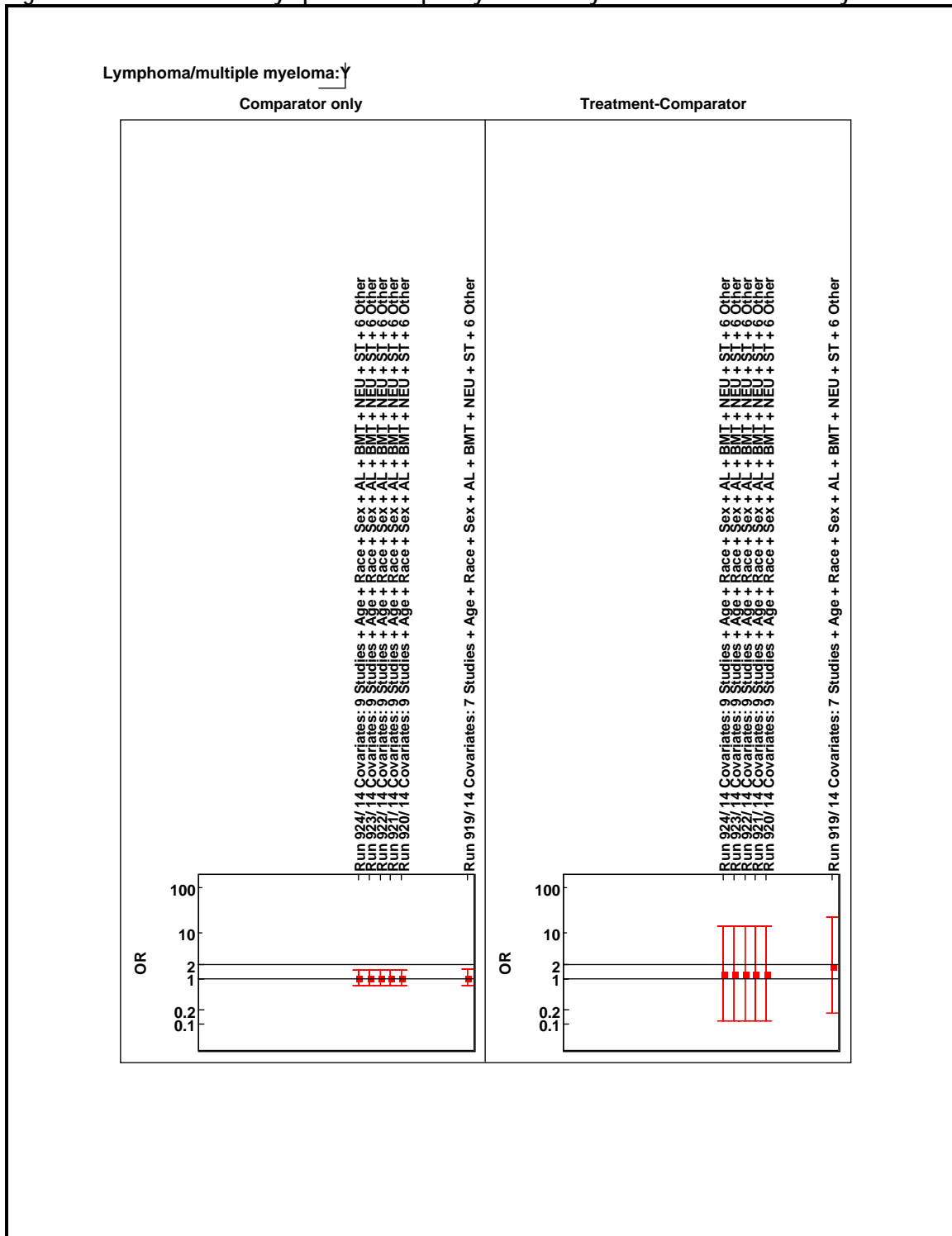
Figure 116: OR values for "Lymphoma/multiple myeloma:N" by runs and covariates analyzed

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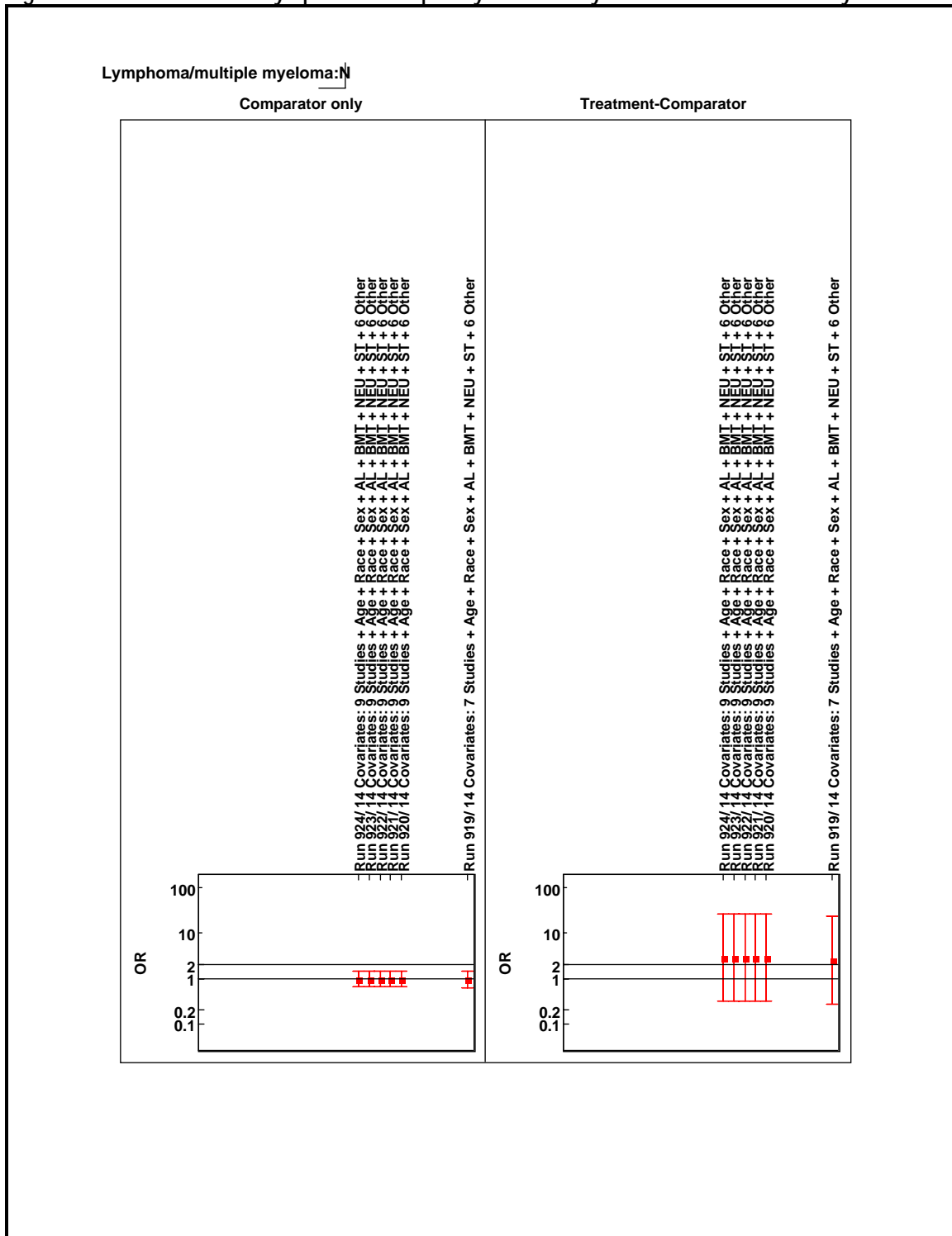
Figure 117: OR values for "Solid tumor:Y" by runs and covariates analyzed
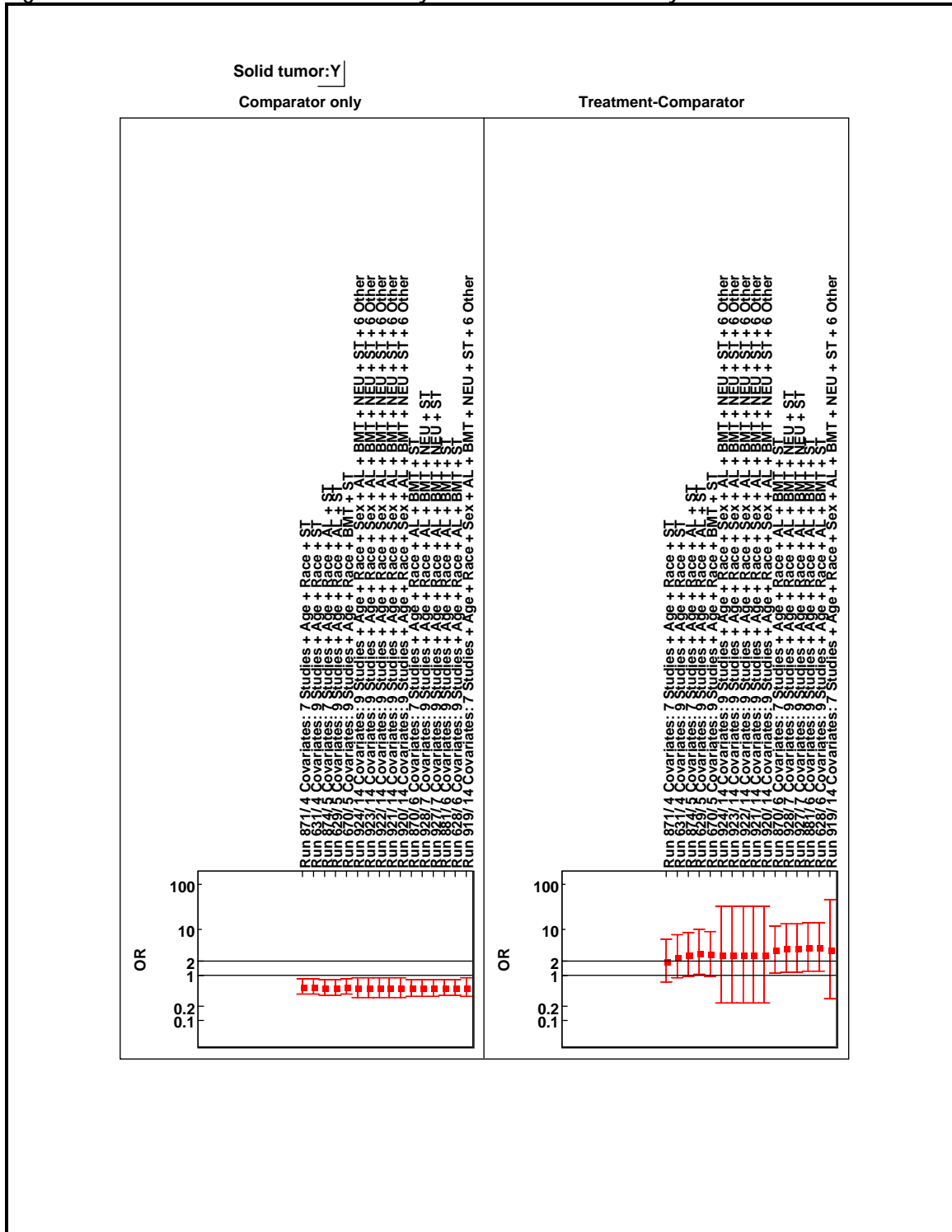
Figure 118: OR values for "Solid tumor:N" by runs and covariates analyzed
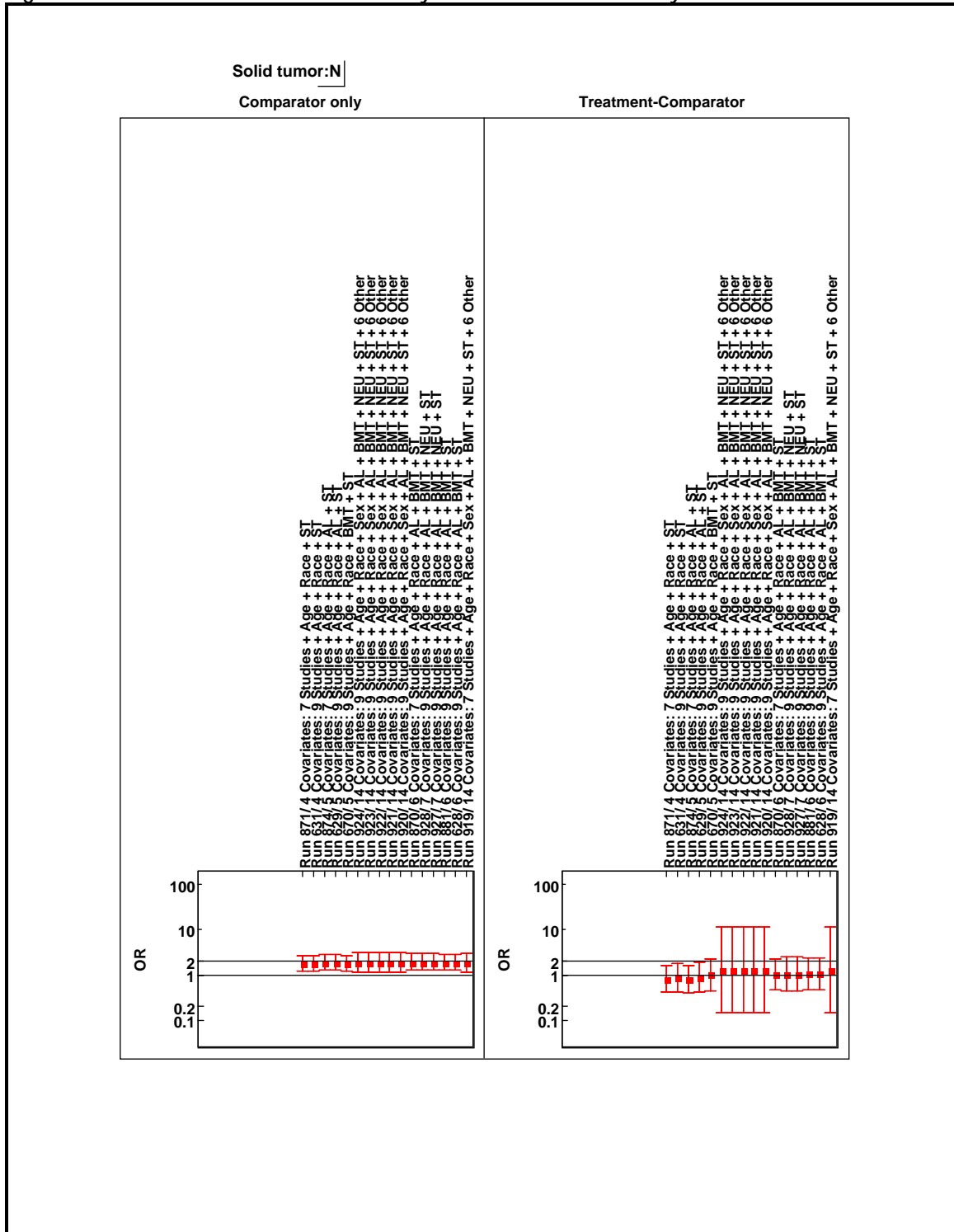
Figure 119: OR values for "Acute leukemia:Y" by runs and covariates analyzed
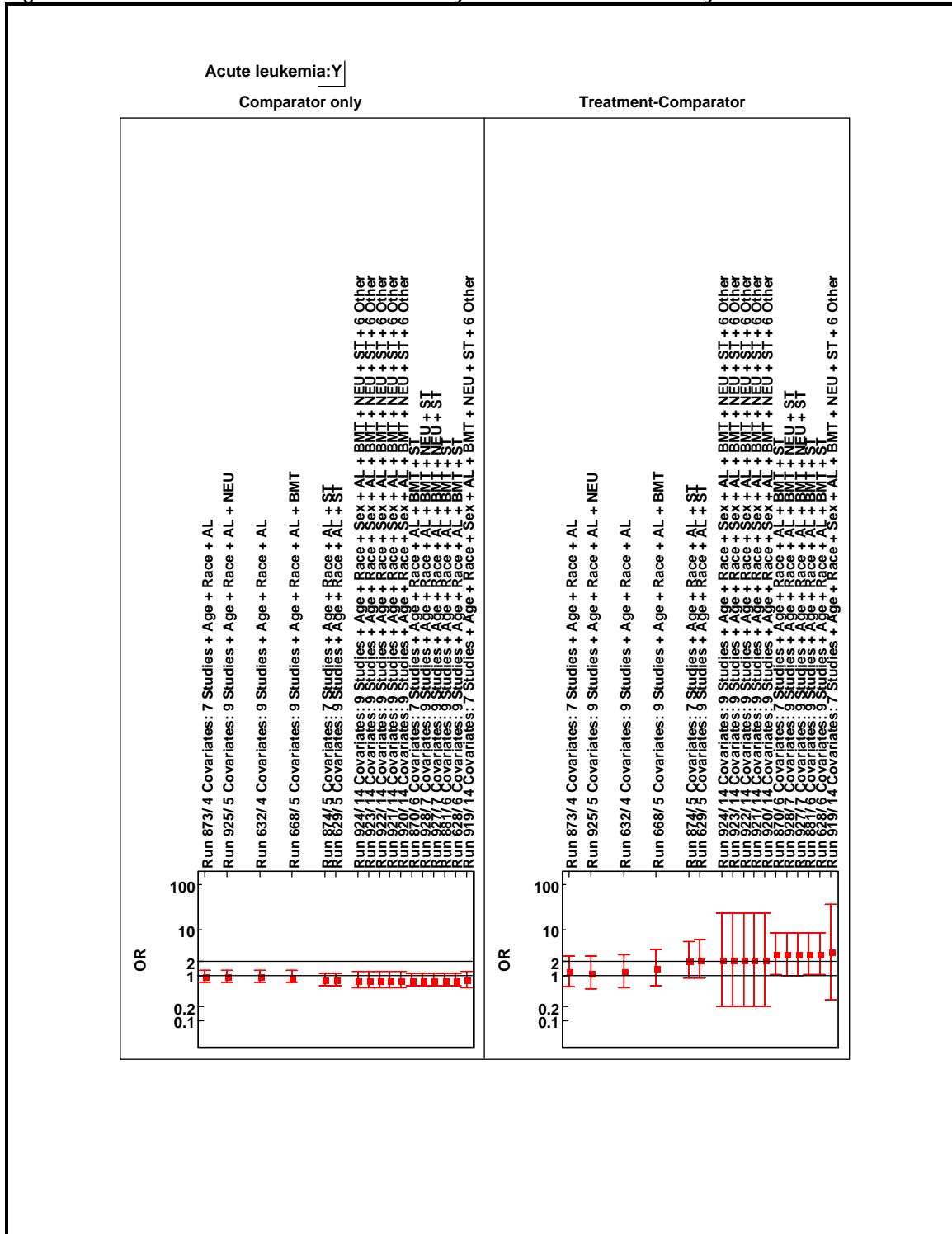
Figure 120: OR values for "Acute leukemia:N" by runs and covariates analyzed
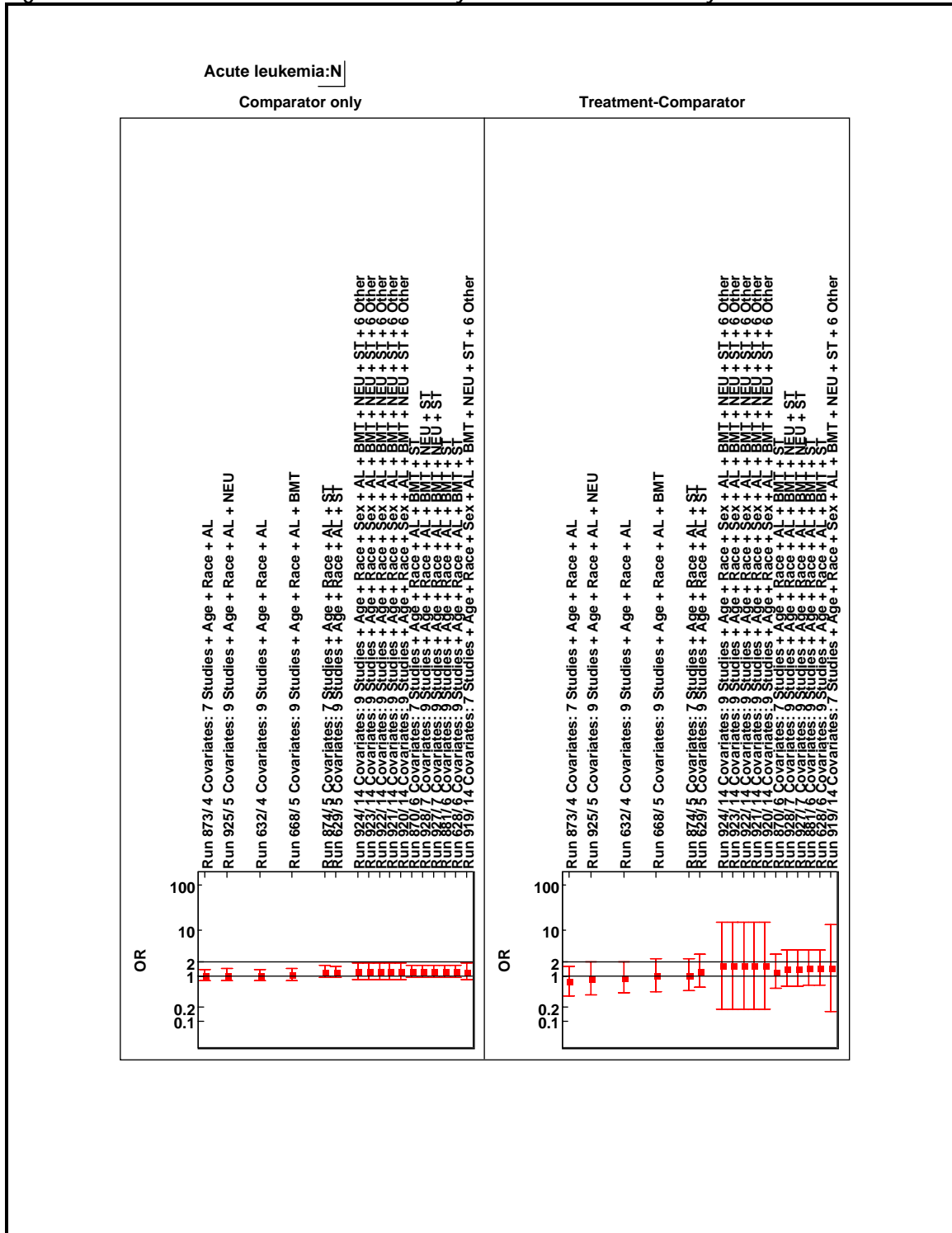
Figure 121: OR values for "Age:<=17" by runs and covariates analyzed
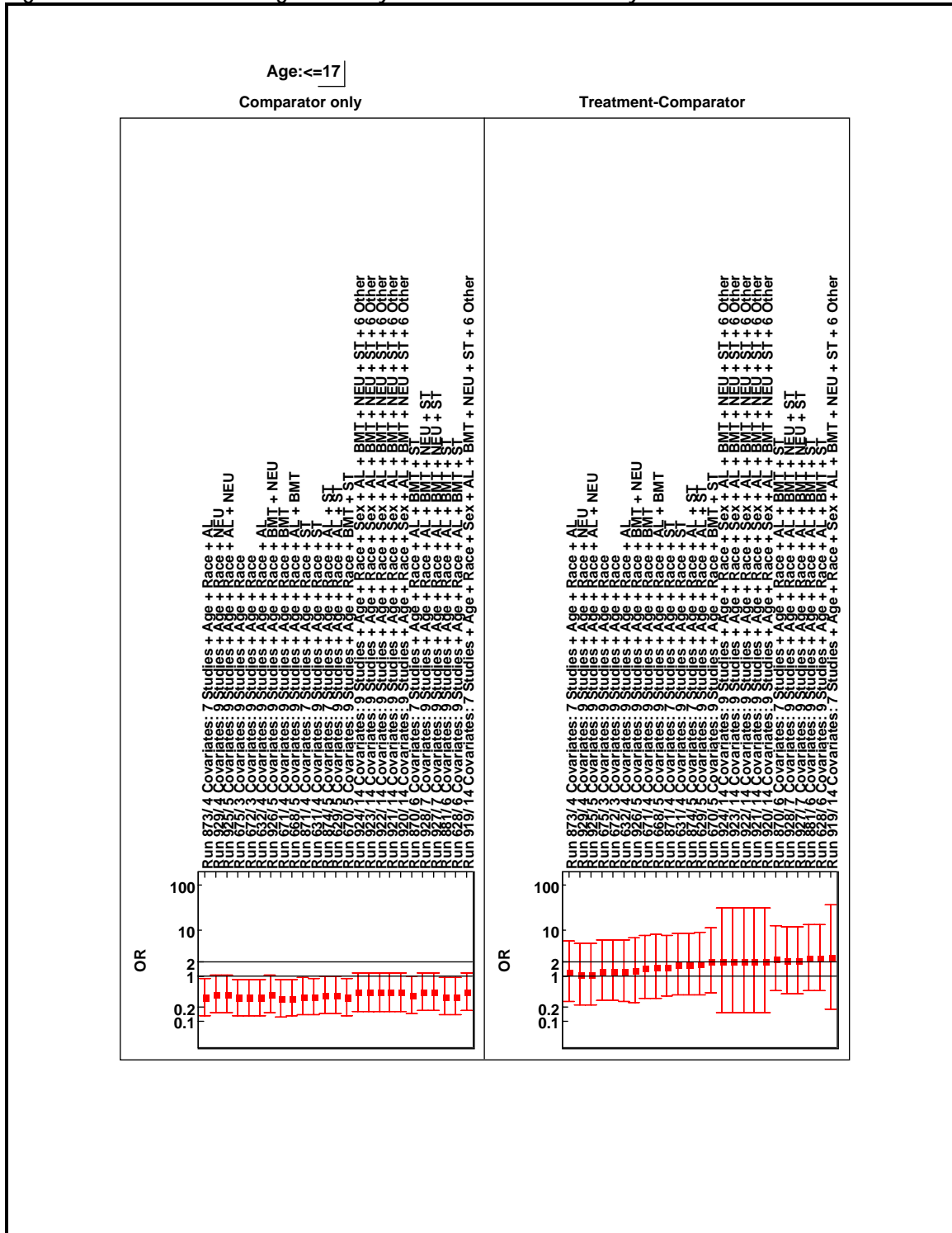
Figure 122: OR values for "Age:<=40" by runs and covariates analyzed
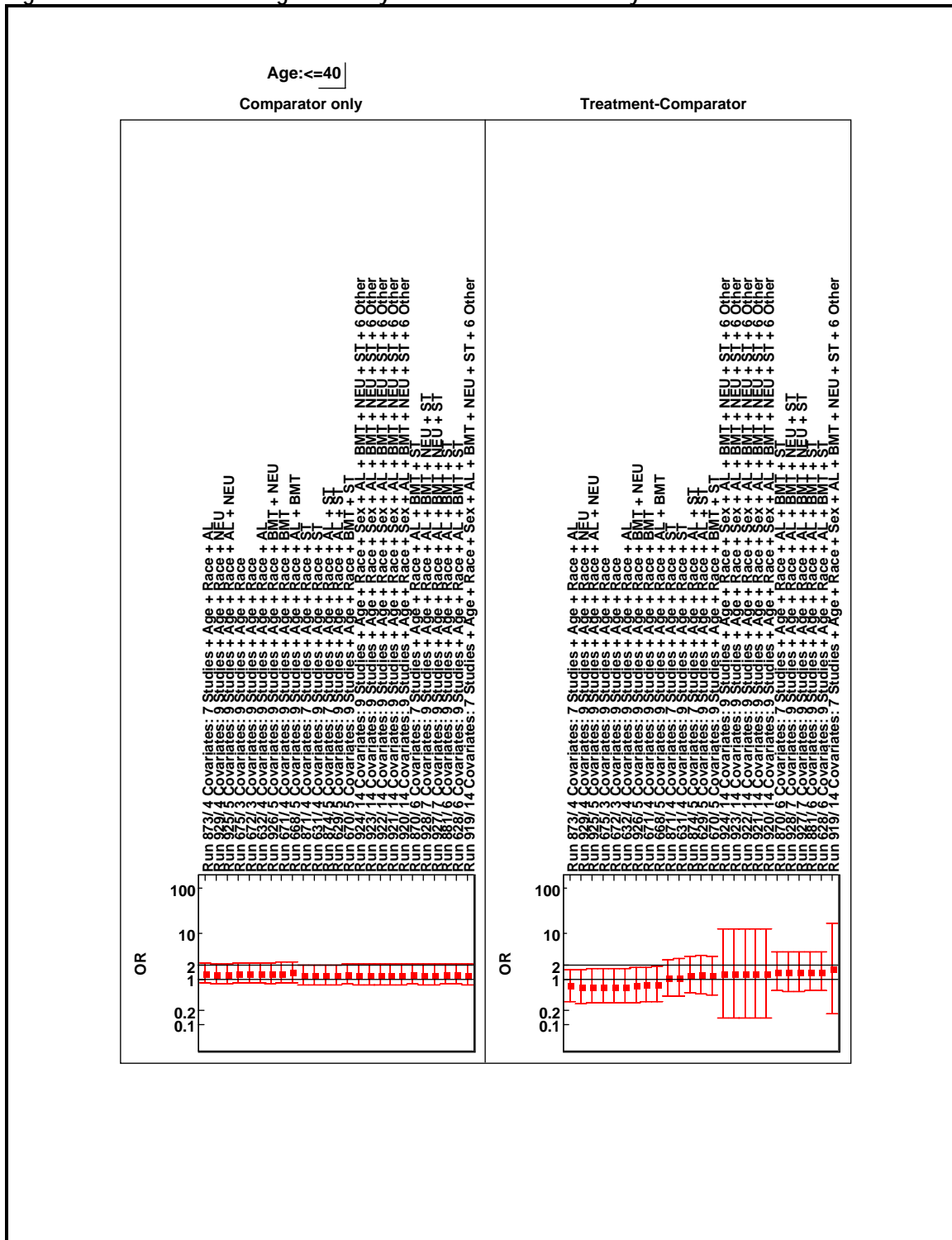
Figure 123: OR values for "Age:<=60" by runs and covariates analyzed
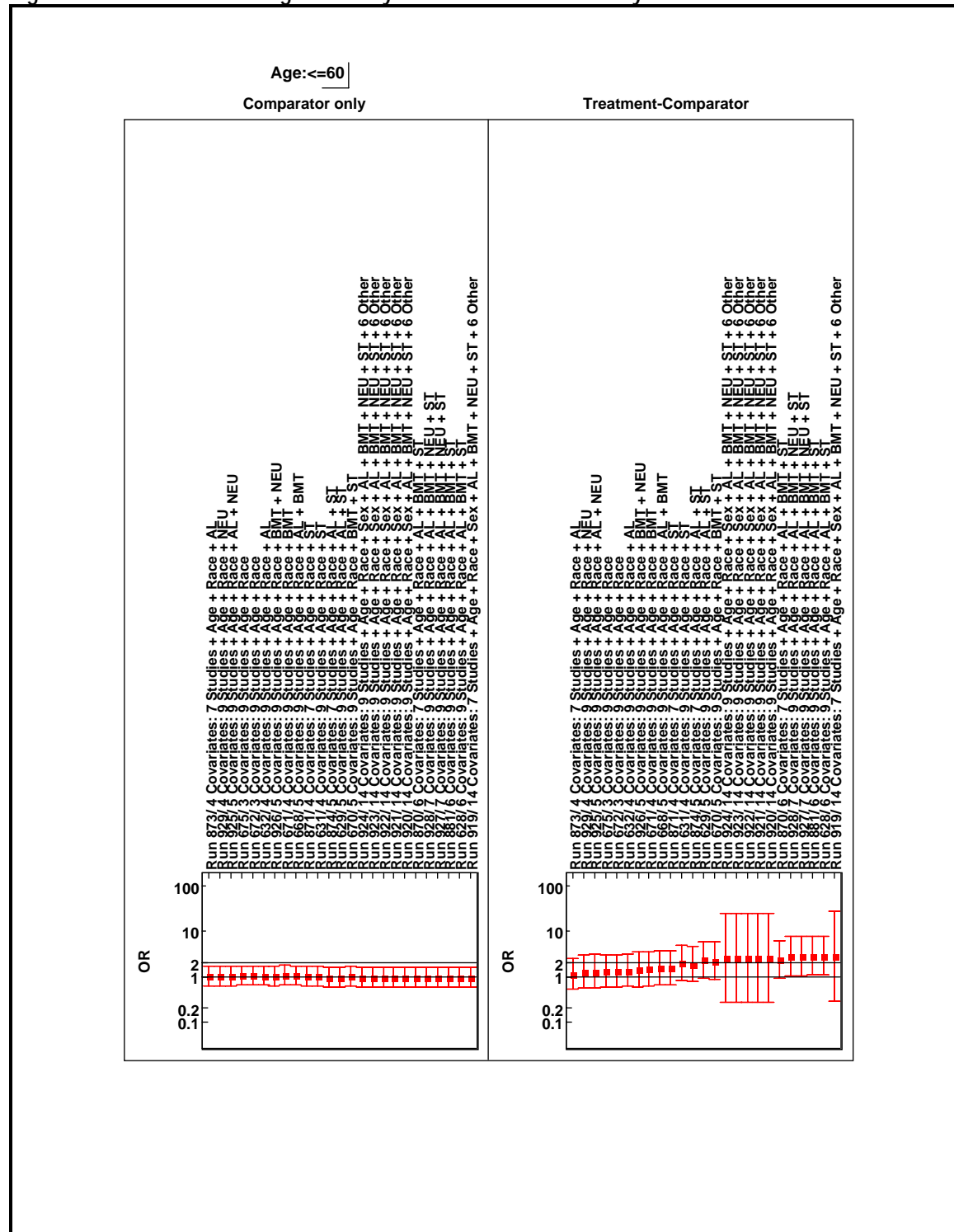
Figure 124: OR values for "Age:>60" by runs and covariates analyzed
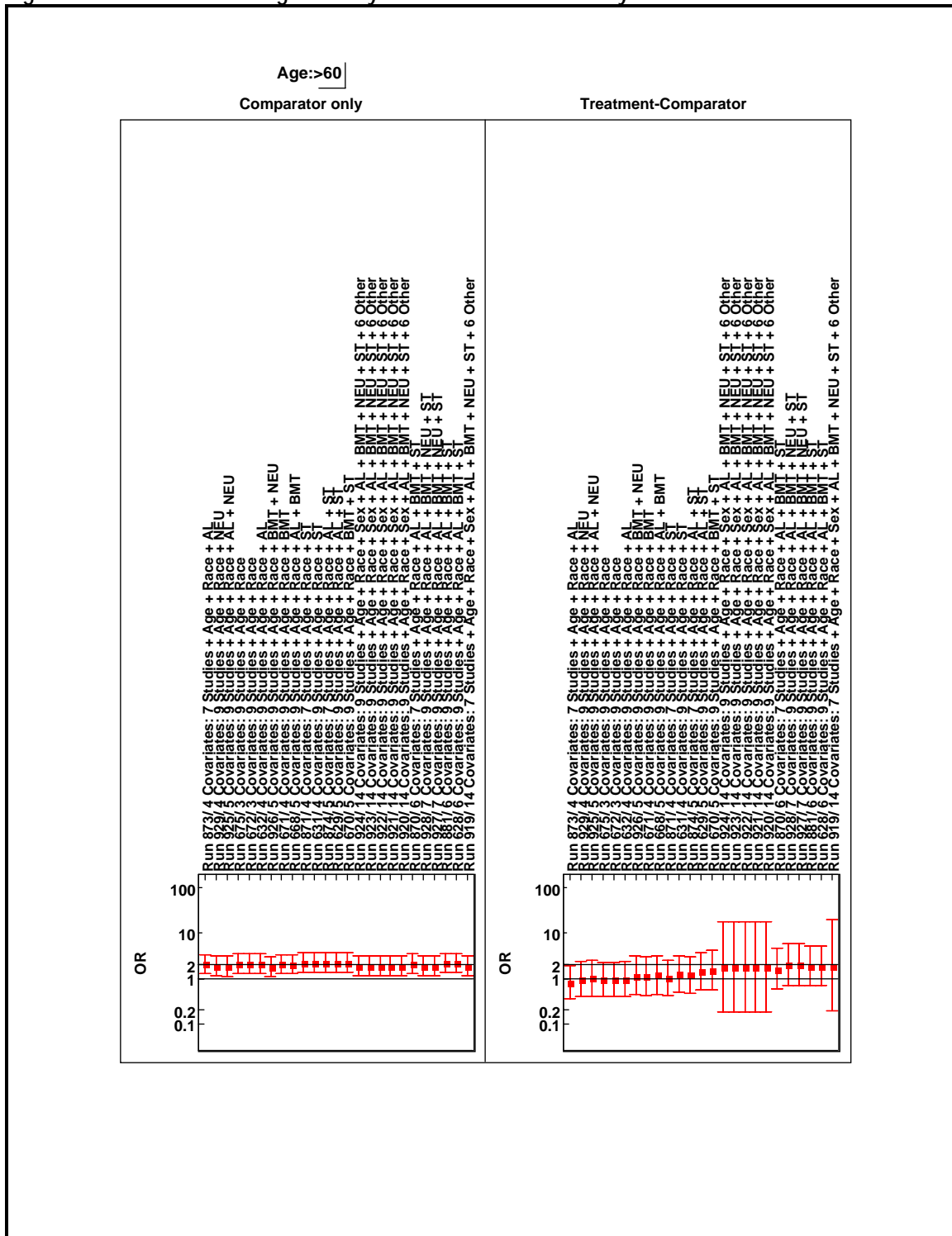
Figure 125: OR values for "Creatinine (2):<=2.5" by runs and covariates analyzed

Figure 126: OR values for "Creatinine (2):>2.5" by runs and covariates analyzed
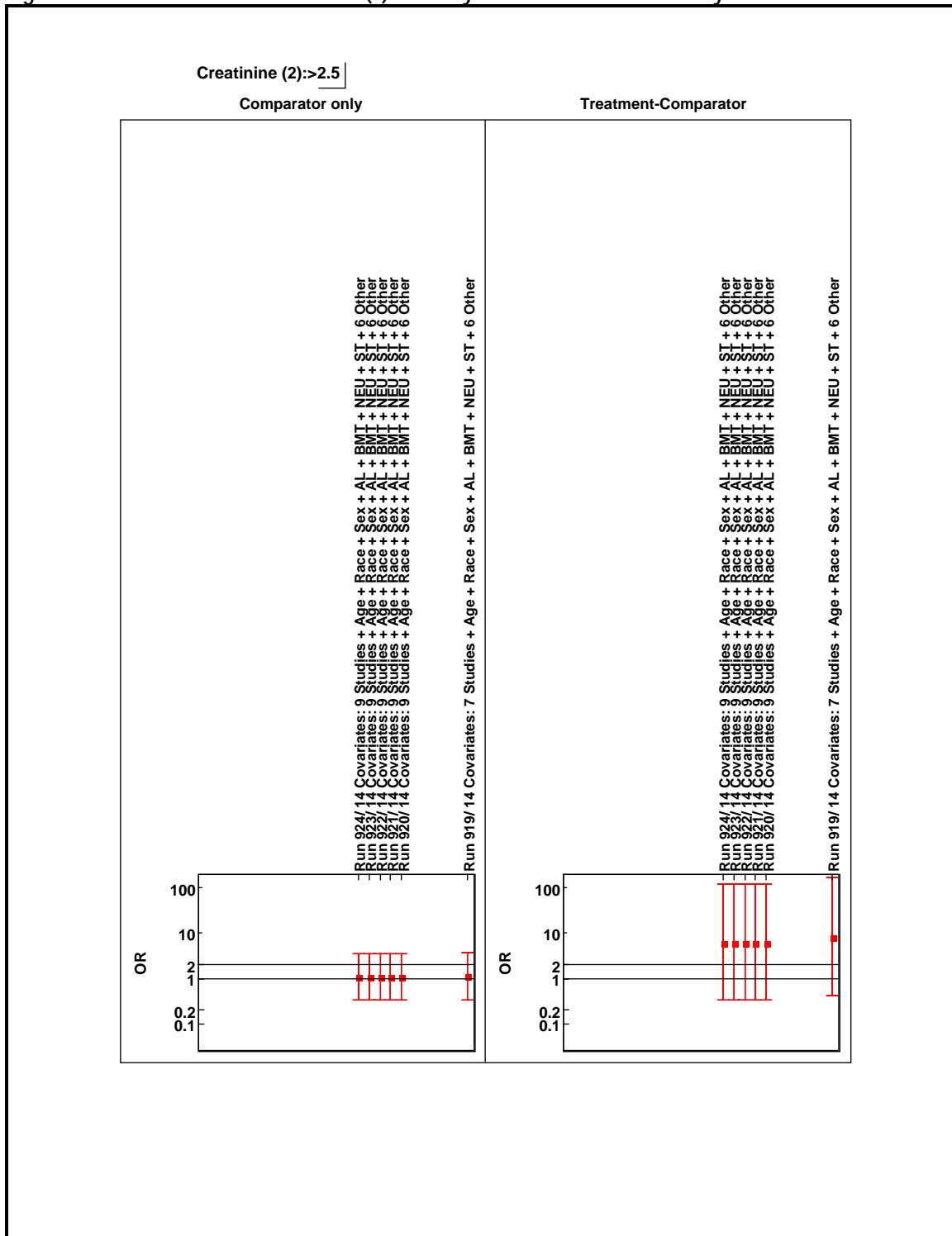
Figure 127: OR values for "Creatinine (2):Not Specified" by runs and covariates analyzed

Figure 128: OR values for "Neutropenia (3):<=100" by runs and covariates analyzed

Figure 129: OR values for "Neutropenia (3):<=500" by runs and covariates analyzed

Figure 130: OR values for "Neutropenia (3):>500" by runs and covariates analyzed
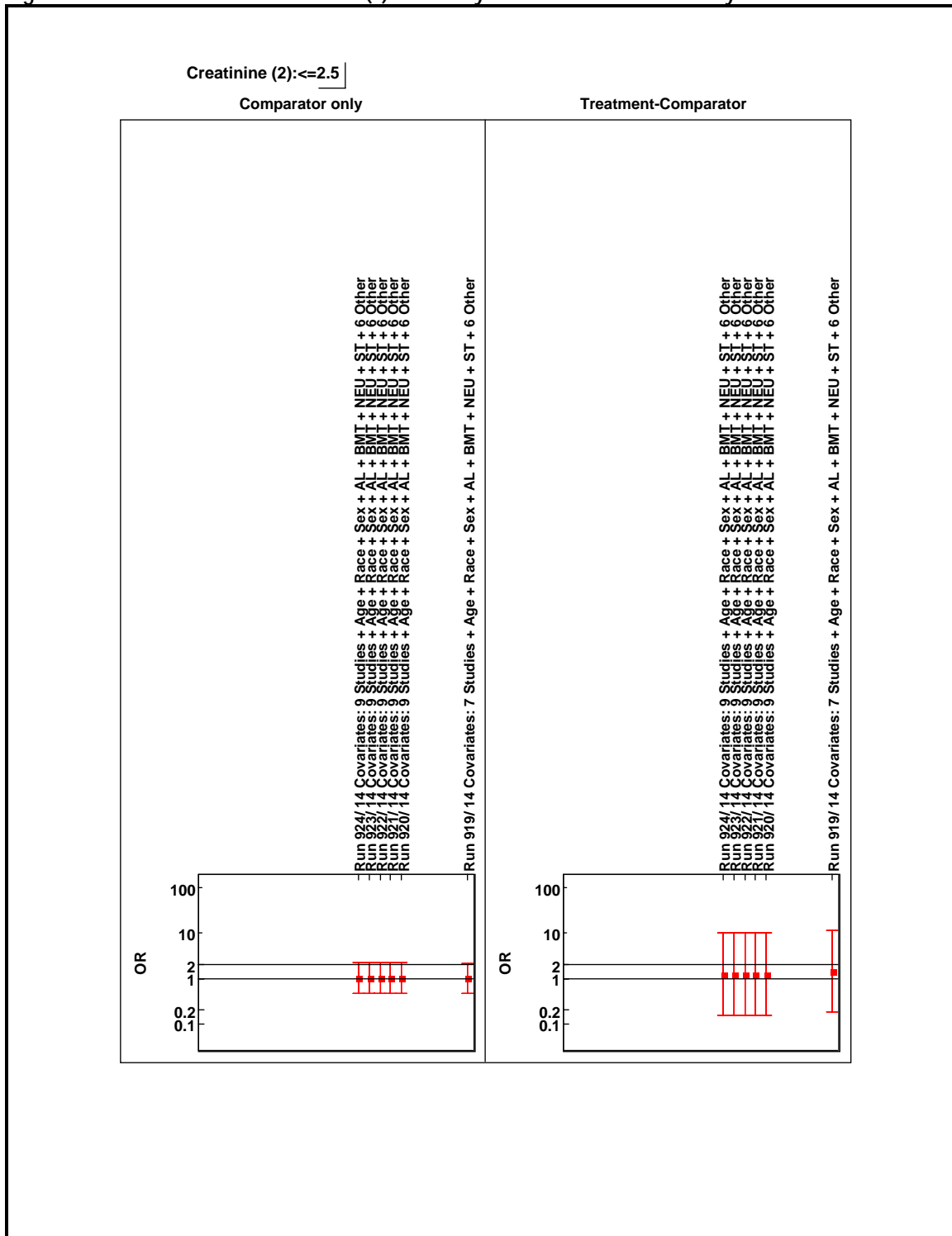
Figure 131: OR values for "Neutropenia (3):Not Specified" by runs and covariates analyzed
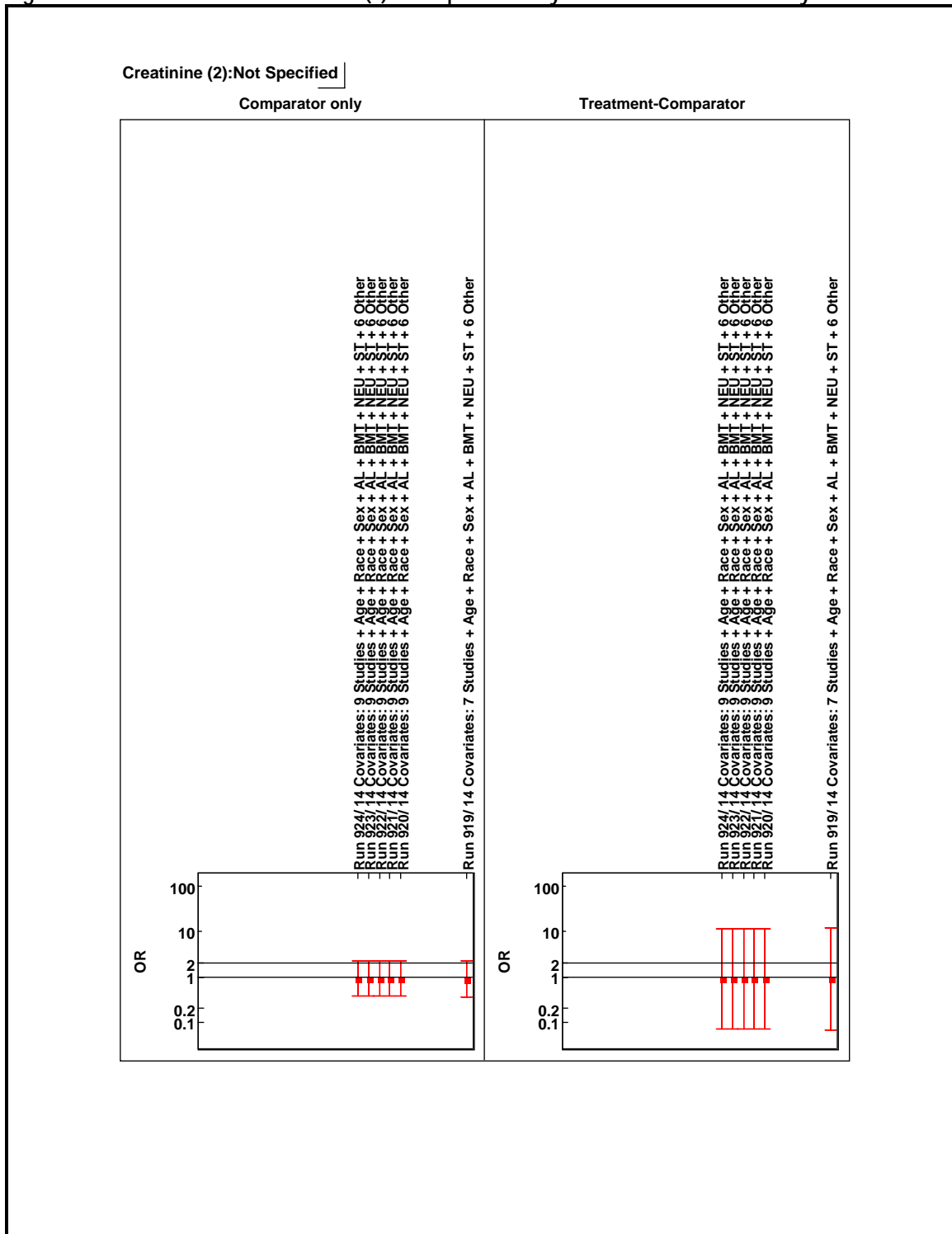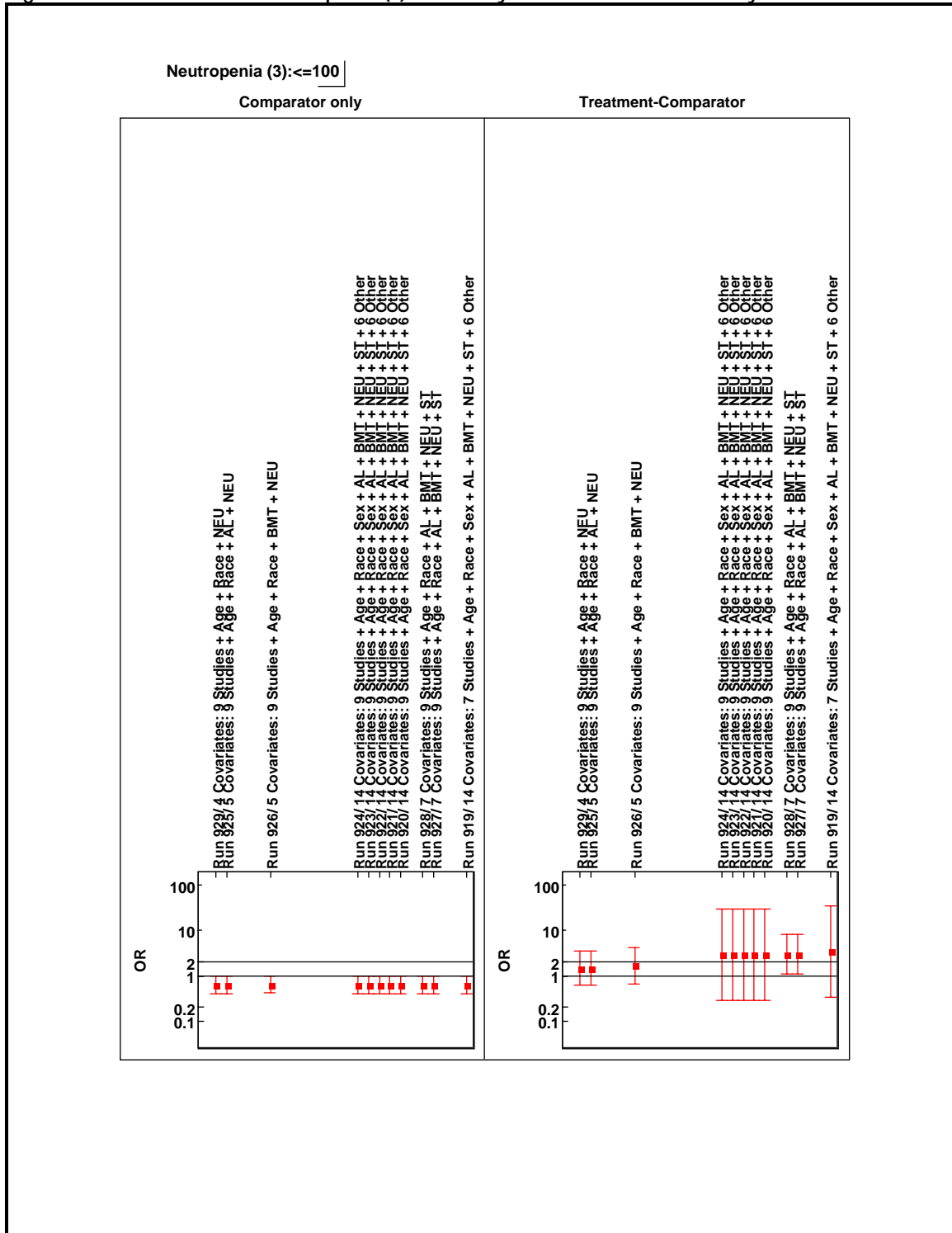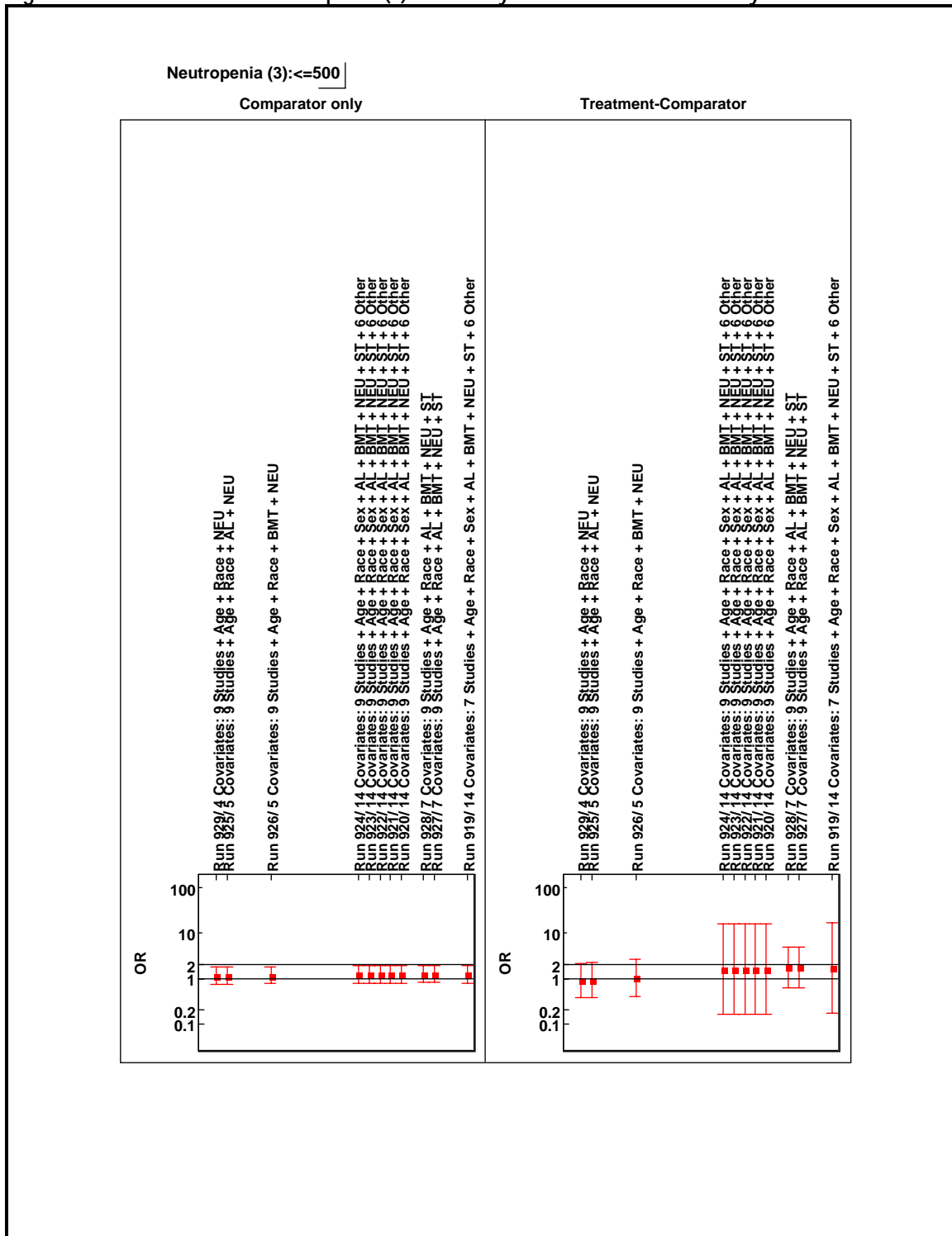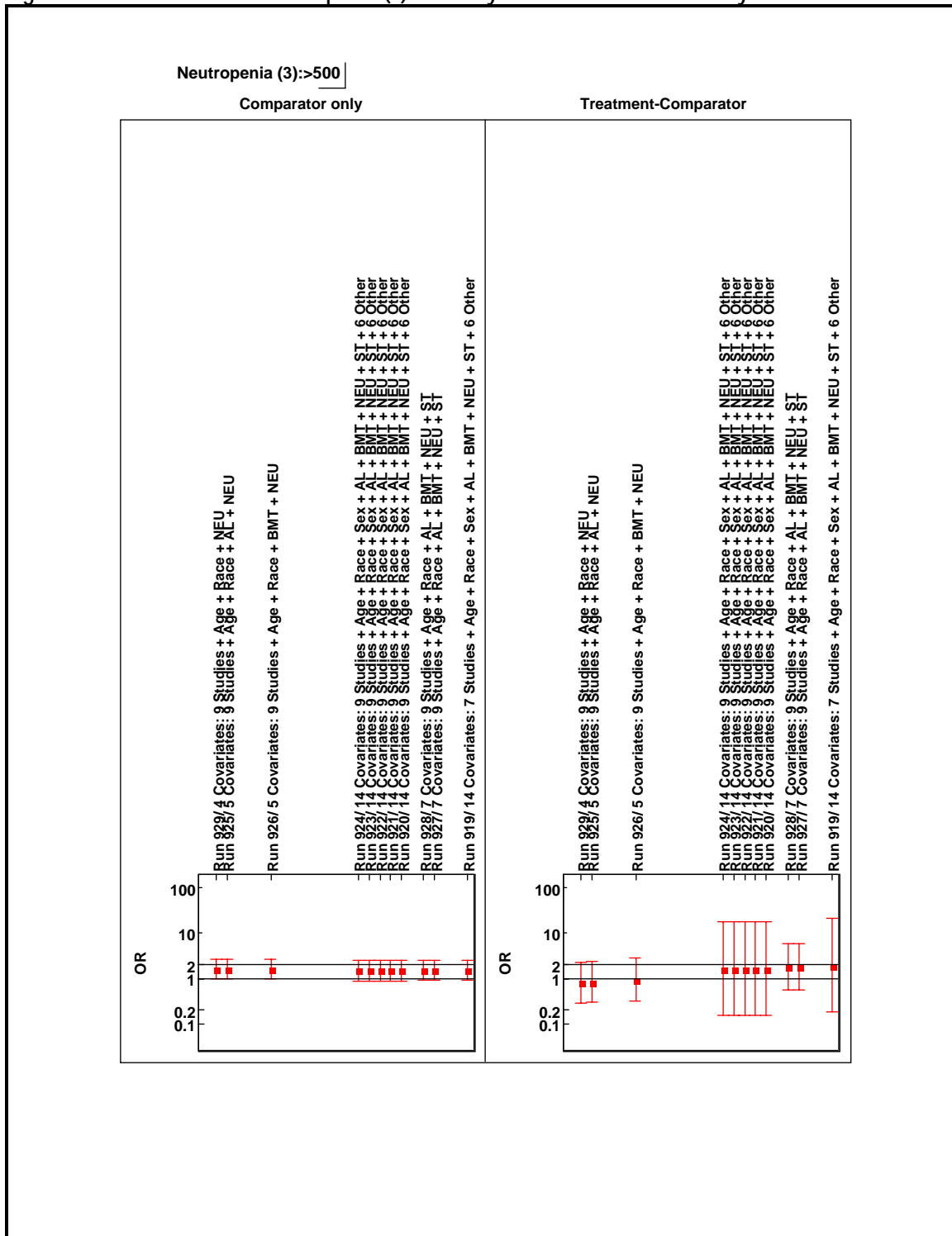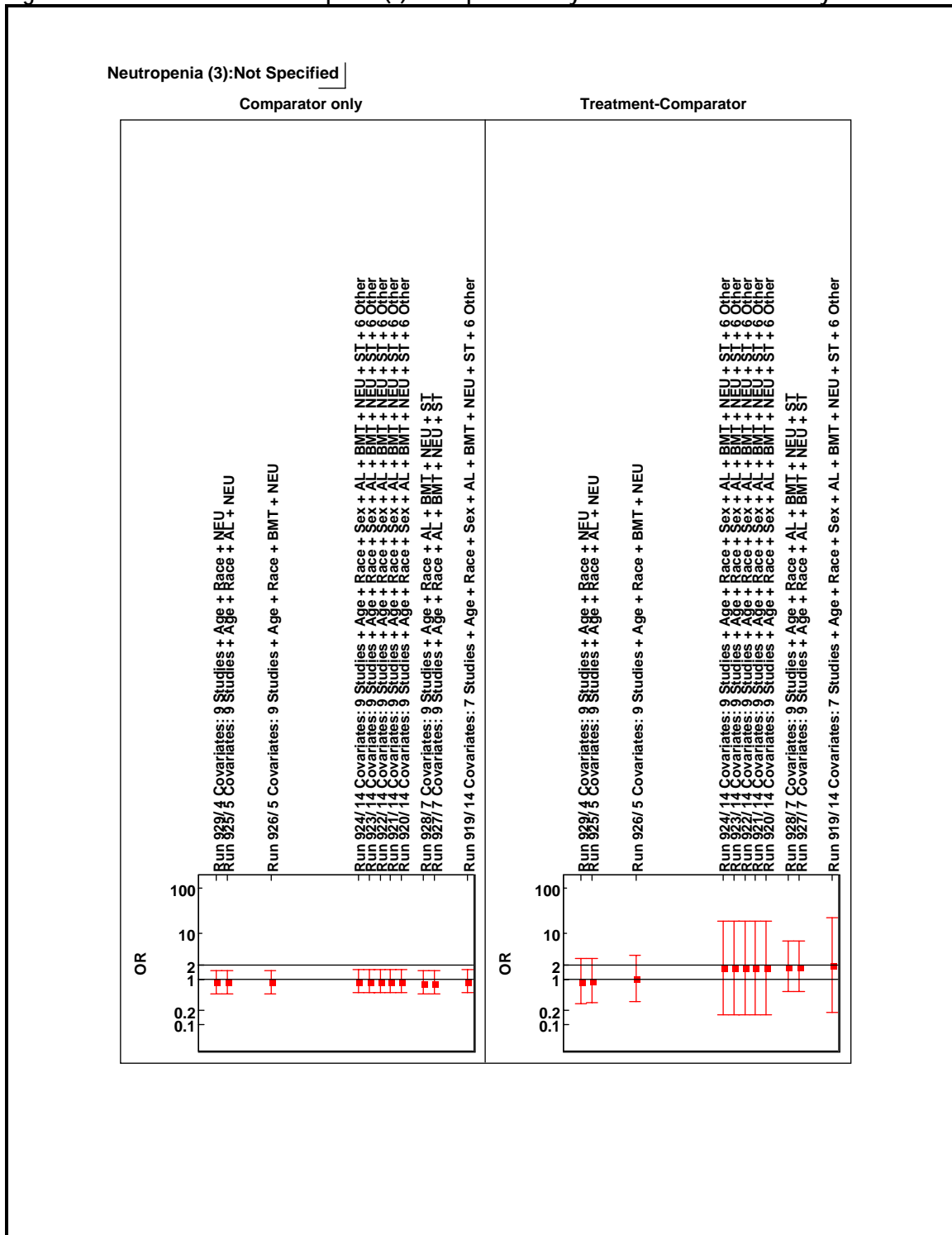
4.16. *Details of Several MBLR Outputs*

The MBLR analysis used in this review is complicated—it models multiple responses, multiple covariates in addition to the treatment effect, and it has the extra complication of a model with interaction terms between treatment and covariates.(9)

The model assesses main effects of covariates plus their treatment interactions. WebSDM CTSD provides graphs and tables of the MBLR results.

The MBLR run generates "Adjusted Effects of Covariates within the Comparator Arm" and "Adjusted Effects of Treatment, Overall and for Subgroups" (9). The first set of graph and table focuses the covariate effects solely within comparator subjects and the second set on treatment-comparator differences.

4.16.1. *Run 920*

Run 920 included 14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + ST + 7 Other] but 2 Issues: Death + 1 CEF Issue (HCC)]. The SMQ HCC was a top event within the syndromic cluster #34 associated with the PT 'Death' with an empirical Bayes OR of 5.95 (0.1,338.25) and a syndromic OR of 4.36 (See Figure 41 and Figure 44)

Figure 132: Audit trail of the configuration used in run 920 (plus 9 studies)

Help

Configuration options for the selected BLR run:

Dosing

Arm of last randomization {Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime'; Comparator includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';}

Predictors

Age:
  Age {<=17 <= 17.0; 17.0 < <=40 <= 40.0; 40.0 < <=60 <= 60.0; 60.0 < >60;}

Sex:
  Sex {F includes: 'F'; M includes: 'M';}

Race:
  Race {Other includes: 'H', 'O', 'X'; Black includes: 'B'; White includes: 'W';}

Concomitant Medications:
  Anti-microbial medication {Antimicrobial medication includes: 'Concomitant Antimicrobial Medication', 'Post Study Antimicrobial Therapy';}
  Bone marrow transplant {Bone marrow transplant includes: 'Bone Marrow Transplant';}
  Surgical procedure {Surgical procedure includes: 'Concomitant/Post Therapy Surgical Procedures';}

Medical History:
  Diabetes mellitus {Diabetes mellitus includes: 'DIABETES MELLITUS', 'Other: GLUCIDIC INTOLERANCE DIAGNOSED';}
  Renal impairment {Renal impairment includes: 'Other: LOW GRADE RENAL INSUFFICIENCY', 'Other: IMPAIRED KIDNEY FUNCTION', 'Other: NON-FUNC L/KIDNEY';}
  Lymphoma/multiple myeloma {Key MHs includes: 'MALIGNANT LYMPHOMAS', 'NON-HODG LYMPHOMA,MULT MYELOMA', 'Other: CHEMOTHERAPY FOR MALIGNANT LYM', 'MULTIPLE MYELOMA', 'MDS + MULTIPLE MYELOMA';}
  Solid tumor {Solid tumor includes: 'ALIMENTARY TRACT CANCER', 'BREAST CANCER', 'CANCER OF ENDOCRINE GLANDS', 'CANCER OF UNKNOWN ORIGIN', 'LUNG CANCER', 'MALE GENITAL CANCER', 'Other: CANCER PAIN', 'Other: CHRONIC CANCER PAIN', 'UROLOGIC CANCER', 'BONE TUMORS', 'CENTRAL NERVOUS SYSTEM TUMORS', 'HEAD AND NECK TUMORS', 'Other: SOLID TUMOR OF THE RENAL PAREN', 'Other: YOLK SAC TUMOR', 'TUMORS OF FEMALE REPR.ORGANS', 'TUMORS OF THE EYE', 'MALIGNANT MELANOMA', 'NEUROBLASTOMA', 'Other: NEUROBLASTOMA', 'SOFT TISSUE SARCOMA', 'Other: ADENOCARCINOMA OF UNKNOWN PRIM', 'Other: SQ CELL CARCINOMA ANAL CANAL', 'UNDIFFERENTIATED CARCINOMA (ME', 'Other: METASTATIC LESION BEHIND RIGHT', 'CA OF MAJOR DIGESTIVE GLANDS', 'Other: NEOPLASTIC DISEASE';}
  Acute leukemia {Acute leukemia includes: '10.92 ACUTE MYELOID LEUKEMIA', '5.12.92 ACUTE MYELOID LEUKEMIA', 'ACUTE BIPHENOTYPIC LEUKAEMIA', 'ACUTE MEYLOID LEUKEMIA', 'ACUTE MYCLOBLASTIC LEUKEMIA M1', 'ACUTE MYCLOID LEUKEMIA', 'ACUTE MYELOBLASTIC LEUCEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA M1', 'ACUTE MYELOBLASTIC LEUKEMIA M5', 'ACUTE MYELOGENOUS LEUKEMIA', 'ACUTE MYELOGENOUS LEUKEMIA M2', 'ACUTE MYELOGENSUS LEUKEMIA', 'ACUTE MYELOIC LEUKAEMIA', 'ACUTE MYELOID LEUCAEMIA', 'ACUTE MYELOID LEUCEMIA (RABM3', 'ACUTE MYELOID LEUKAEMIA', 'ACUTE MYELOID LEUKAEMIA (M1)', 'ACUTE MYELOID LEUKAEMIA (M7)', 'ACUTE MYELOID LEUKAEMIA - MI', 'ACUTE MYELOID LEUKAEMIA M5', 'ACUTE MYELOID LEUKEMIA', 'ACUTE MYELOID LEUKEMIA (AML M1', 'ACUTE MYELOID LEUKEMIA (HYPER', 'ACUTE MYELOID LEUKEMIA (M3)', 'ACUTE MYELOID LEUKEMIA (MX)', 'ACUTE MYELOID LEUKEMIA M2', 'ACUTE MYELOID LEUKEMIA SINCE 1', 'ACUTE MYELOID LEUKEMIA ST POST', 'ACUTE MYELOID LEUKEMIA,TYPE M5', 'ACUTE MYELOIDE LEUKEMIA', 'ACUTE MYLOID LEUKEMIA', 'ACUTE MYLOID LEUKEMIA', 'AML-ACUTE MYELOGENOUS WITH MONOCYTIC SUBTYPE', 'LMA NY/ACUTE MYELOID LEUKEMIA', 'MACUTE MYELOID LEUKEMIA VERY', 'MYLEODYSPLASTC DISORDER EVOLVING INTO ACUTE LEUKEMIA', 'RELAPSED ACUTE MYELOIDLEUCHEMI', 'AML', 'AML - M3', 'AML - M5', 'AML - M5A', 'AML - MSQ DIAGNOSED 11/92', 'AML AFTER MDS-RAC-T, NOW RELAP', 'AML DIAGNOSED 060593', 'AML DIAGNOSED 2/92,NOW 2ND REL', 'AML FAB M6', 'AML M1', 'AML M3', 'AML M4', 'AML M5', 'AML M5A', 'AML OF M4-M5SUBTYPE', 'AML RELAPSE', 'AML SEC TO MYELOPROEIFERATIVE', 'AML SINCE 7/92 AFTER MOS (TY', 'AML, TYPE PROMYELOID', 'AML-M2', 'AML-M2 WITH TRANSLOCATION', 'AML-M5A', 'AML-MS DIAGNOSED 1/93', 'AML-MSA', 'MDS-AML', 'RAEB-T -> AML', 'AC MYELOID LEUKEMIA', 'LEUKEMIA : ALL', 'LEUKEMIA : ANLL', 'BLASTIC TRANSFORM OF MYELODYSP', 'MYELODYSPLASTIC SYNDROME IN BL', 'ACUTATIVE OF CHRONIC MYELOMONO';}

Baseline Labs:
  Creatinine (2) {<=2.5 <= 2.5; 2.5 < >2.5;}
  Neutropenia (3) {<=100 <= 0.1; 0.1 < <=500 <= 0.5; 0.5 < >500;}

Issues

PT: Death {MedDRA PT Disproportionality (Death) - from Issue Cluster 'Cluster #34'}
SMQ: Haemorrhagic cerebrovascular conditions [narrow] {Standard MedDRA Query (SMQ) Disproportionality (Haemorrhagic cerebrovascular conditions [narrow])...}

Options

  Issues occurring any time

Figure 133: Display options for each issue in run 920

Figure 134: Overall estimates for all the issues in run 920
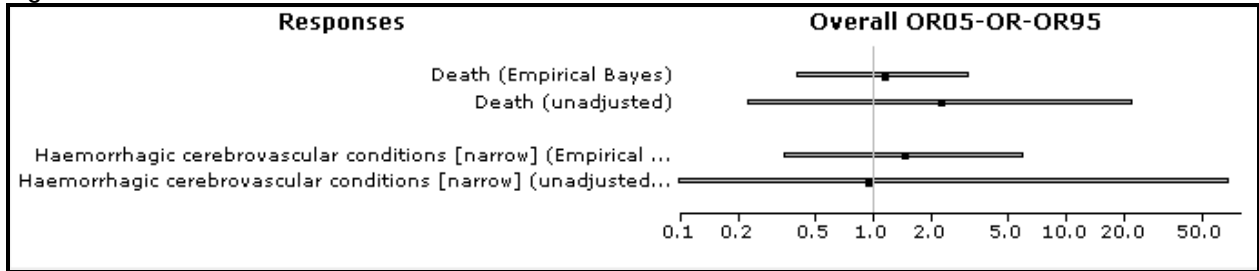
Table 19: Overall estimates for all the issues in run 920

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Death					
Bayesian	-1	Overall	0.413	1.12	3.039
Unadjusted	-1	Overall	0.229	2.204	21.217
Haemorrhagic cerebrovascular conditions [narrow]					
Bayesian	-1	Overall	0.353	1.432	5.806
Unadjusted	-1	Overall	0.013	0.928	65.915

Figure 135: Adjusted (left column) and Unadjusted (right column) Comparing Covariate Subgroups within the Comparator Arm (Issue = 'Death', Run 920)
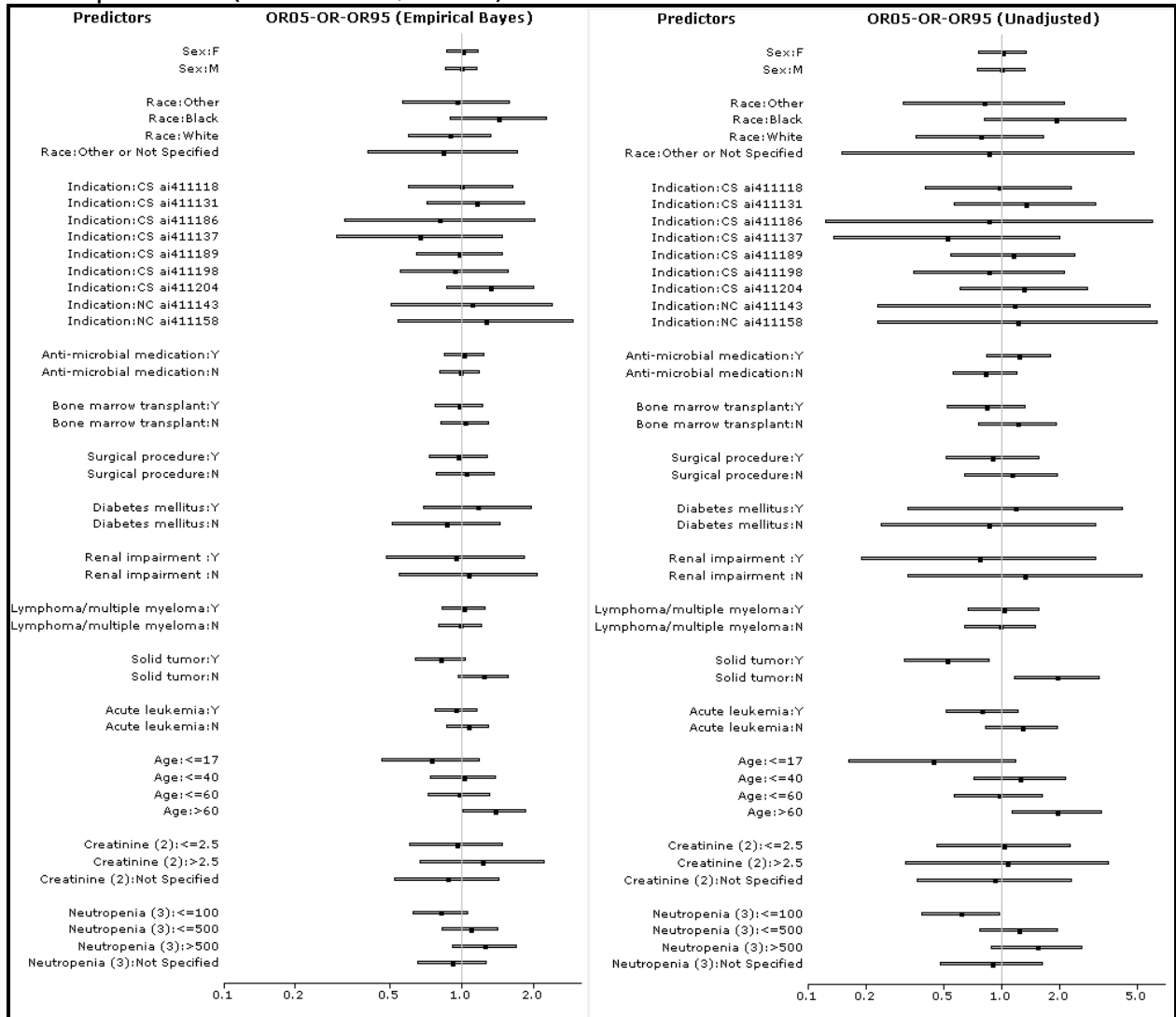
Figure 136: Adjusted (left column) and Unadjusted (right column) Treatment-Comparator Odds Ratios, Overall and for Covariate Subgroups (Issue = 'Death', Run 920)
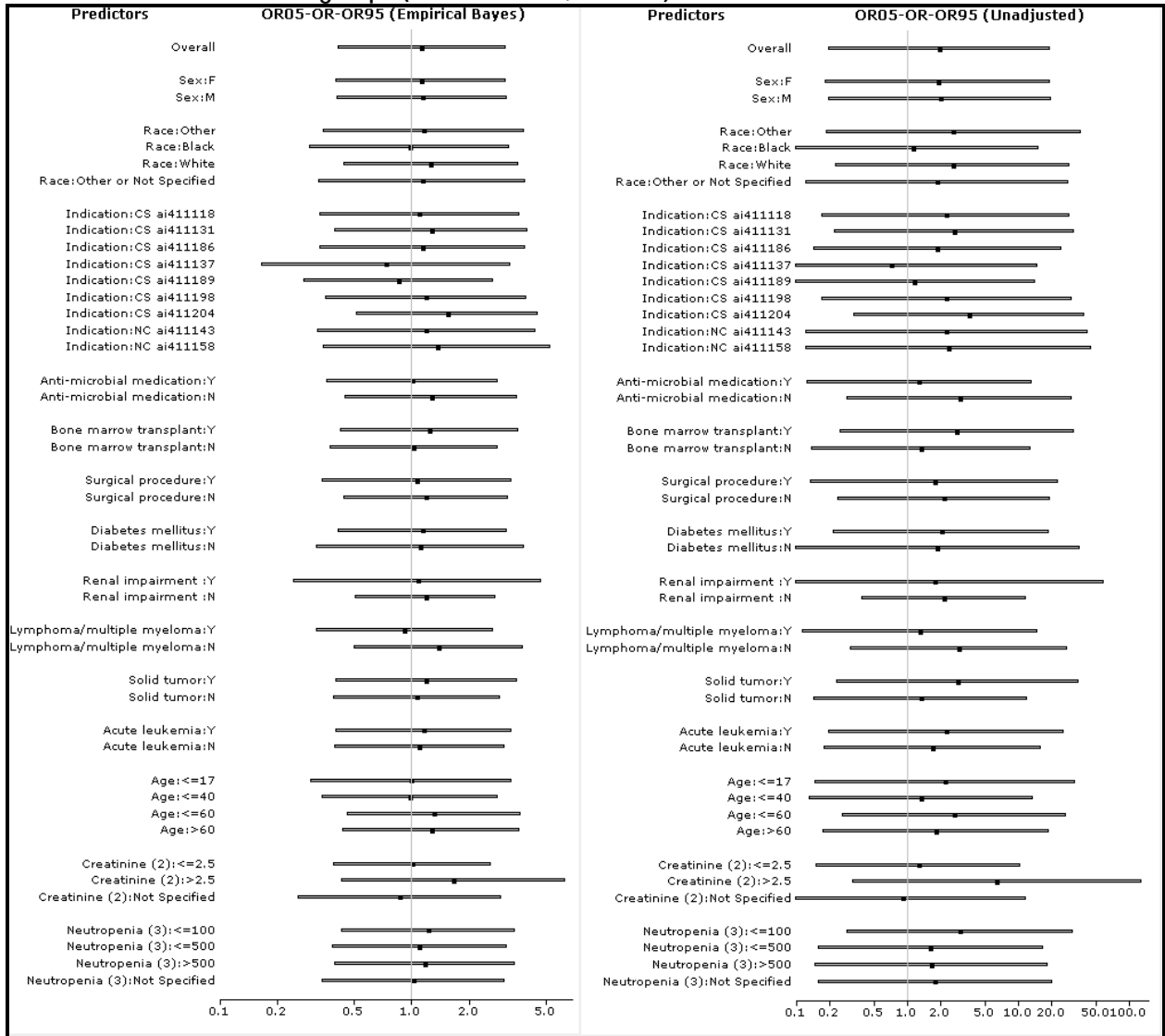
Table 20: Odds Ratios for death by covariate subgroups within the comparator arm (Issue = 'Death', run 920)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Sex:F	0.877	1.007	1.156	0.769	1.009	1.325	52	620
Sex:M	0.865	0.993	1.14	0.755	0.991	1.301	62	782
Race:Other	0.572	0.948	1.571	0.316	0.808	2.064	7	92
Race:Black	0.904	1.423	2.241	0.822	1.886	4.323	11	66
Race:White	0.606	0.892	1.313	0.365	0.771	1.629	79	908
Race:Other or Not Specified	0.406	0.83	1.698	0.153	0.852	4.746	17	336
Indication:CS ai411118	0.604	0.989	1.62	0.41	0.963	2.261	9	107
Indication:CS ai411131	0.72	1.145	1.82	0.581	1.32	2.996	15	179
Indication:CS ai411186	0.326	0.807	1.996	0.125	0.857	5.861	17	336
Indication:CS ai411137	0.303	0.666	1.464	0.139	0.522	1.963	1	70
Indication:CS ai411189	0.65	0.977	1.47	0.555	1.143	2.353	18	263
Indication:CS ai411198	0.557	0.93	1.551	0.355	0.859	2.079	8	103
Indication:CS ai411204	0.872	1.315	1.984	0.614	1.298	2.745	34	242
Indication:NC ai411143	0.509	1.1	2.375	0.232	1.151	5.709	8	76
Indication:NC ai411158	0.544	1.252	2.884	0.232	1.199	6.184	4	26
Anti-microbial medication:Y	0.854	1.02	1.219	0.85	1.222	1.756	70	774
Anti-microbial medication:N	0.821	0.98	1.171	0.569	0.818	1.176	44	628
Bone marrow transplant:Y	0.784	0.975	1.214	0.535	0.833	1.297	19	321
Bone marrow transplant:N	0.824	1.025	1.276	0.771	1.201	1.871	95	1081
Surgical procedure:Y	0.736	0.964	1.262	0.522	0.894	1.532	7	61
Surgical procedure:N	0.792	1.038	1.359	0.653	1.118	1.916	107	1341
Diabetes mellitus:Y	0.695	1.161	1.939	0.333	1.169	4.1	97	1066
Diabetes mellitus:N	0.516	0.862	1.439	0.244	0.855	3	17	336
Renal impairment :Y	0.49	0.942	1.81	0.193	0.763	3.023	0	3
Renal impairment :N	0.553	1.062	2.04	0.331	1.31	5.186	114	1399
Lymphoma/multiple myeloma:Y	0.839	1.017	1.233	0.68	1.017	1.522	30	423
Lymphoma/multiple myeloma:N	0.811	0.983	1.192	0.657	0.983	1.471	84	979
Solid tumor:Y	0.643	0.811	1.023	0.318	0.521	0.852	23	284
Solid tumor:N	0.977	1.232	1.554	1.173	1.92	3.143	91	1118
Acute leukemia:Y	0.778	0.942	1.14	0.521	0.787	1.19	46	584
Acute leukemia:N	0.877	1.062	1.285	0.84	1.27	1.92	68	818
Age:<=17	0.466	0.739	1.174	0.166	0.439	1.161	4	108
Age:<=40	0.748	1.012	1.37	0.725	1.231	2.092	28	421
Age:<=60	0.729	0.973	1.3	0.578	0.964	1.607	43	571
Age:>60	1.026	1.373	1.837	1.143	1.919	3.223	39	302
Creatinine (2):<=2.5	0.614	0.95	1.472	0.468	1.019	2.216	108	1324
Creatinine (2):>2.5	0.674	1.215	2.19	0.326	1.068	3.497	2	6
Creatinine (2):Not Specified	0.529	0.866	1.416	0.374	0.919	2.257	4	72
Neutropenia (3):<=100	0.629	0.811	1.044	0.392	0.613	0.957	45	687
Neutropenia (3):<=500	0.839	1.084	1.402	0.784	1.221	1.903	35	363
Neutropenia (3):>500	0.926	1.247	1.68	0.891	1.512	2.565	19	145
Neutropenia (3):Not Specified	0.663	0.912	1.255	0.488	0.884	1.603	15	207

Table 21: Treatment-comparator Odds Ratios for death, Overall and by covariate (Issue = 'Death', run 920)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Overall	0.417	1.12	3.004	0.201	1.918	18.27	73	817
Sex:F	0.408	1.113	3.036	0.189	1.87	18.471	34	374
Sex:M	0.415	1.126	3.057	0.203	1.967	19.01	39	443
Race:Other	0.353	1.15	3.748	0.19	2.57	34.761	5	58
Race:Black	0.299	0.97	3.151	0.088	1.127	14.392	4	31
Race:White	0.447	1.251	3.498	0.234	2.535	27.505	51	499
Race:Other or Not Specified	0.333	1.125	3.807	0.126	1.842	26.873	13	229
Indication:CS ai411118	0.336	1.091	3.537	0.174	2.203	27.827	5	54
Indication:CS ai411131	0.405	1.257	3.899	0.225	2.6	30.029	9	95
Indication:CS ai411186	0.336	1.135	3.836	0.147	1.851	23.357	13	229
Indication:CS ai411137	0.167	0.729	3.178	0.035	0.704	14.237	0	35
Indication:CS ai411189	0.277	0.85	2.607	0.098	1.149	13.468	8	136
Indication:CS ai411198	0.359	1.177	3.86	0.173	2.236	28.947	5	49
Indication:CS ai411204	0.524	1.525	4.435	0.34	3.561	37.265	21	117
Indication:NC ai411143	0.327	1.185	4.29	0.124	2.219	39.852	8	76
Indication:NC ai411158	0.352	1.346	5.143	0.125	2.311	42.781	4	26
Anti-microbial medication:Y	0.364	0.998	2.736	0.127	1.262	12.582	40	422
Anti-microbial medication:N	0.457	1.256	3.454	0.294	2.913	28.889	33	395
Bone marrow transplant:Y	0.429	1.229	3.521	0.252	2.772	30.453	14	195
Bone marrow transplant:N	0.379	1.02	2.746	0.141	1.326	12.458	59	622
Surgical procedure:Y	0.347	1.06	3.233	0.139	1.748	21.973	4	32
Surgical procedure:N	0.451	1.183	3.102	0.241	2.103	18.359	69	785
Diabetes mellitus:Y	0.421	1.134	3.059	0.223	2.001	17.967	60	588
Diabetes mellitus:N	0.323	1.105	3.777	0.099	1.838	34.1	13	229
Renal impairment :Y	0.247	1.069	4.638	0.054	1.737	55.75	0	2
Renal impairment :N	0.513	1.172	2.677	0.399	2.117	11.223	73	815
Lymphoma/multiple myeloma:Y	0.321	0.91	2.583	0.116	1.282	14.165	14	249
Lymphoma/multiple myeloma:N	0.511	1.377	3.713	0.312	2.869	26.411	59	568
Solid tumor:Y	0.409	1.186	3.445	0.238	2.813	33.241	18	152
Solid tumor:N	0.396	1.057	2.816	0.148	1.307	11.584	55	665
Acute leukemia:Y	0.408	1.146	3.219	0.201	2.213	24.419	32	354
Acute leukemia:N	0.404	1.094	2.96	0.181	1.662	15.25	41	463
Age:<=17	0.303	0.988	3.224	0.152	2.166	30.97	3	57
Age:<=40	0.344	0.969	2.728	0.136	1.332	13.045	17	266
Age:<=60	0.471	1.306	3.622	0.266	2.612	25.686	31	339
Age:>60	0.445	1.256	3.547	0.177	1.794	18.194	22	155
Creatinine (2):<=2.5	0.395	0.998	2.52	0.154	1.242	10.002	69	771
Creatinine (2):>2.5	0.439	1.639	6.121	0.333	6.341	120.863	2	2
Creatinine (2):Not Specified	0.259	0.858	2.842	0.071	0.895	11.211	2	44
Neutropenia (3):<=100	0.438	1.214	3.367	0.29	2.915	29.318	33	401
Neutropenia (3):<=500	0.391	1.094	3.064	0.161	1.605	15.955	21	214
Neutropenia (3):>500	0.4	1.161	3.37	0.153	1.645	17.705	10	81
Neutropenia (3):Not Specified	0.346	1.019	2.999	0.161	1.757	19.141	9	121

4.16.2. Run 924

Run 924 included the 14 Covariates: 9 Studies + Age + Race + Sex + AL + BMT + ST + 7 Other] but with 5 issues associated with Death *in the comparator arm* [6 Issues: Death + 5 COMP Issues (AD + HT + J + R + BD)].

Figure 137: Audit trail of the configuration used in run 924 (plus 9 studies)

Configuration options for the selected BLR run:

Dosing

Arm of last randomization {Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime'; Comparator includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';}

Predictors

Age:
Age {<=17 <= 17.0; 17.0 < <=40 <= 40.0; 40.0 < <=60 <= 60.0; 60.0 < >60;}

Sex:
Sex {F includes: 'F'; M includes: 'M';}

Race:
Race {Other includes: 'H', 'O', 'X'; Black includes: 'B'; White includes: 'W';}

Concomitant Medications:
Anti-microbial medication {Antimicrobial medication includes: 'Concomitant Antimicrobial Medication', 'Post Study Antimicrobial Therapy';}
Bone marrow transplant {Bone marrow transplant includes: 'Bone Marrow Transplant';}
Surgical procedure {Surgical procedure includes: 'Concomitant/Post Therapy Surgical Procedures';}

Medical History:
Diabetes mellitus {Diabetes mellitus includes: 'DIABETES MELLITUS', 'Other: GLUCIDIC INTOLERANCE DIAGNOSED';}
Renal impairment {Renal impairment includes: 'Other: LOW GRADE RENAL INSUFFICIENCY', 'Other: IMPAIRED KIDNEY FUNCTION', 'Other: NON-FUNC L/KIDNEY';}
Lymphoma/multiple myeloma {Key MHs includes: 'MALIGNANT LYMPHOMAS', 'NON-HODG LYMPHOMA,MULT MYELOMA', 'Other: CHEMOTHERAPY FOR MALIGNANT LYM', 'MULTIPLE MYELOMA', 'MDS + MULTIPLE MYELOMA';}
Solid tumor {Solid tumor includes: 'ALIMENTARY TRACT CANCER', 'BREAST CANCER', 'CANCER OF ENDOCRINE GLANDS', 'CANCER OF UNKNOWN ORIGIN', 'LUNG CANCER', 'MALE GENITAL CANCER', 'Other: CANCER PAIN', 'Other: CHRONIC CANCER PAIN', 'UROLOGIC CANCER', 'BONE TUMORS', 'CENTRAL NERVOUS SYSTEM TUMORS', 'HEAD AND NECK TUMORS', 'Other: SOLID TUMOR OF THE RENAL PAREN', 'Other: YOLK SAC TUMOR', 'TUMORS OF FEMALE REPR.ORGANS', 'TUMORS OF THE EYE', 'MALIGNANT MELANOMA', 'NEUROBLASTOMA', 'Other: NEUROBLASTOMA', 'SOFT TISSUE SARCOMA', 'Other: ADENOCARCINOMA OF UNKNOWN PRIM', 'Other: SQ CELL CARCINOMA ANAL CANAL', 'UNDIFFERENTIATED CARCINOMA (ME', 'Other: METASTATIC LESION BEHIND RIGHT', 'CA OF MAJOR DIGESTIVE GLANDS', 'Other: NEOPLASTIC DISEASE';}
Acute leukemia {Acute leukemia includes: '10.92 ACUTE MYELOID LEUKEMIA', '5.12.92 ACUTE MYELOID LEUKEMIA', 'ACUTE BIPHENOTYPIC LEUKAEMIA', 'ACUTE MEYLOID LEUKAEMIA', 'ACUTE MYCLOBLASTIC LEUKEMIA M1', 'ACUTE MYCLOID LEUKEMIA', 'ACUTE MYELOBLASTIC LEUCEMIA', 'ACUTE MYELOBLASTIC LEUKAEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA', 'ACUTE MYELOBLASTIC LEUKEMIA M1', 'ACUTE MYELOBLASTIC LEUKEMIA M5', 'ACUTE MYELOGENOUS LEUKEMIA', 'ACUTE MYELOGENOUS LEUKEMIA M2', 'ACUTE MYELOGENSUS LEUKEMIA', 'ACUTE MYELOIC LEUKAEMIA', 'ACUTE MYELOID LEUCAEMIA', 'ACUTE MYELOID LEUCEMIA (RABM3', 'ACUTE MYELOID LEUKAEMIA', 'ACUTE MYELOID LEUKAEMIA (M1)', 'ACUTE MYELOID LEUKAEMIA (M7)', 'ACUTE MYELOID LEUKAEMIA - MI', 'ACUTE MYELOID LEUKAEMIA M5', 'ACUTE MYELOID LEUKEMIA', 'ACUTE MYELOID LEUKEMIA (AML M1', 'ACUTE MYELOID LEUKEMIA (HYPER', 'ACUTE MYELOID LEUKEMIA (M3)', 'ACUTE MYELOID LEUKEMIA (MX)', 'ACUTE MYELOID LEUKEMIA M2', 'ACUTE MYELOID LEUKEMIA SINCE 1', 'ACUTE MYELOID LEUKEMIA ST POST', 'ACUTE MYELOID LEUKEMIA,TYPE M5', 'ACUTE MYELOIDE LEUKEMIA', 'ACUTE MYLEOID LEUKEMIA', 'ACUTE MYLOID LEUKEMIA', 'AML-ACUTE MYELOGENOUS WITH MONOCYTIC SUBTYPE', 'LMA NY/ACUTE MYELOID LEUKEMIA', 'MACUTE MYELOID LEUKEMIA VERY', 'MYLEODYSPLASTC DISORDER EVOLVING INTO ACUTE LEUKEMIA', 'RELAPSED ACUTE MYELOIDLEUCHEMI', 'AML', 'AML - M3', 'AML - M5', 'AML - M5A', 'AML - MSQ DIAGNOSED 11/92', 'AML AFTER MDS-RAC-T, NOW RELAP', 'AML DIAGNOSED 060593', 'AML DIAGNOSED 2/92,NOW 2ND REL', 'AML FAB M6', 'AML M1', 'AML M3', 'AML M4', 'AML M5', 'AML M5A', 'AML OF M4-M5SUBTYPE', 'AML RELAPSE', 'AML SEC TO MYELOPROEIFERATIVE', 'AML SINCE 7/92 AFTER MOS (TY', 'AML, TYPE PROMYELOID', 'AML-M2', 'AML-M2 WITH TRANSLOCATION', 'AML-M5A', 'AML-MS DIAGNOSED 1/93', 'AML-MSA', 'MDS-AML', 'RAEB-T -> AML', 'AC MYELOID LEUKEMIA', 'LEUKEMIA : ALL', 'LEUKEMIA : ANLL', 'BLASTIC TRANSFORM OF MYELODYSP', 'MYELODYSPLASTIC SYNDROME IN BL', 'ACUTATIVE OF CHRONIC MYELOMONO';}

Baseline Labs:
Creatinine (2) {<=2.5 <= 2.5; 2.5 < >2.5;}
Neutropenia (3) {<=100 <= 0.1; 0.1 < <=500 <= 0.5; 0.5 < >500;}

Issues

PT: Abdominal distension {MedDRA PT Disproportionality (Abdominal distension) - generated from a run of the $$$BASIC$$$SCRE...}
PT: Death {MedDRA PT Disproportionality (Death) - from Issue Cluster 'Cluster #34'}
PT: Hypertension {MedDRA PT Disproportionality (Hypertension) - generated from a run of the $$$BASIC$$$SCREENING$$$...}
PT: Jaundice {MedDRA PT Disproportionality (Jaundice) - generated from a run of the $$$BASIC$$$SCREENING$$$ ana...}
PT: Rales {MedDRA PT Disproportionality (Rales) - generated from a run of the $$$BASIC$$$SCREENING$$$ analys...}
SMQ: Biliary disorders (SMQ) [broad] {Standard MedDRA Query (SMQ) Disproportionality (Biliary disorders (SMQ) [broad]) - generated from...}

Options

Issues occurring any time

Figure 138: Display options in run 924

Figure 139: Overall estimates for all the issues in run 924
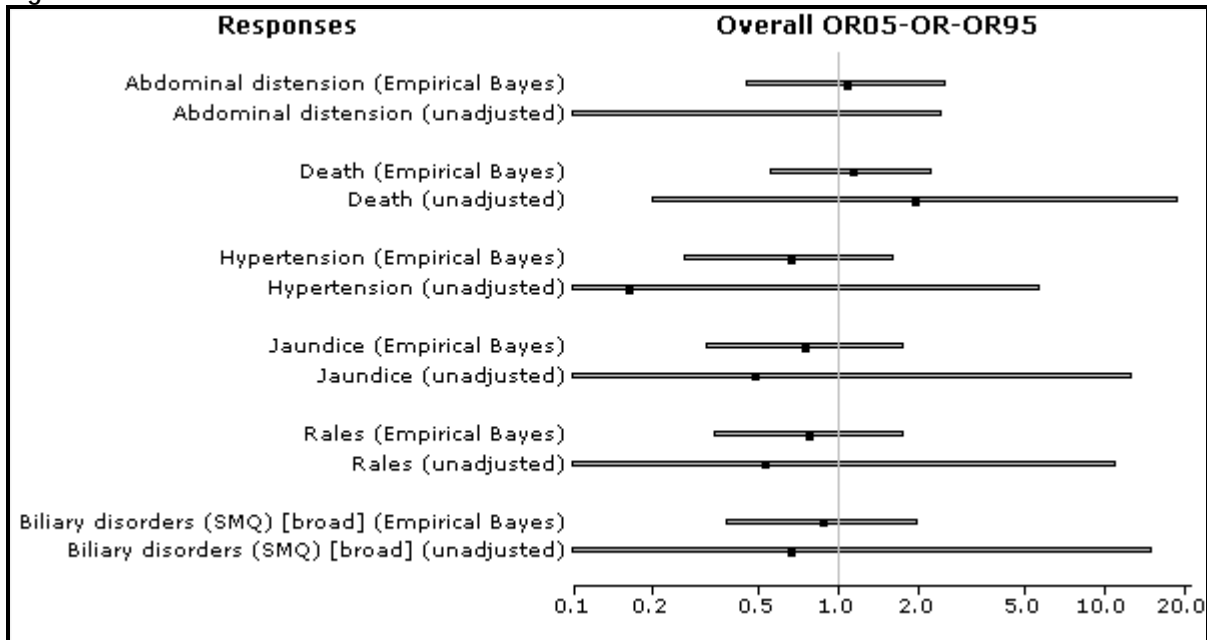
Table 22: Overall estimates for all the issues in run 924

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Abdominal distension					
Empirical Bayes	-1	Overall	0.458	1.065	2.477

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Unadjusted	-1	Overall	0.002	0.074	2.387
Death					
Empirical Bayes	-1	Overall	0.561	1.11	2.196
Unadjusted	-1	Overall	0.201	1.918	18.27
Hypertension					
Empirical Bayes	-1	Overall	0.268	0.649	1.571
Unadjusted	-1	Overall	0.005	0.159	5.558
Jaundice					
Empirical Bayes	-1	Overall	0.321	0.737	1.694
Unadjusted	-1	Overall	0.018	0.478	12.347
Rales					
Empirical Bayes	-1	Overall	0.321	0.737	1.694
Unadjusted	-1	Overall	0.018	0.478	12.347
Biliary disorders (SMQ) [narrow]					
Empirical Bayes	-1	Overall	0.386	0.862	1.925
Unadjusted	-1	Overall	0.029	0.656	14.719

Figure 140: Adjusted (left column) and Unadjusted (right column) Effects of Covariates Subgroups within the Comparator Arm (Issue = 'Death', Run 924)
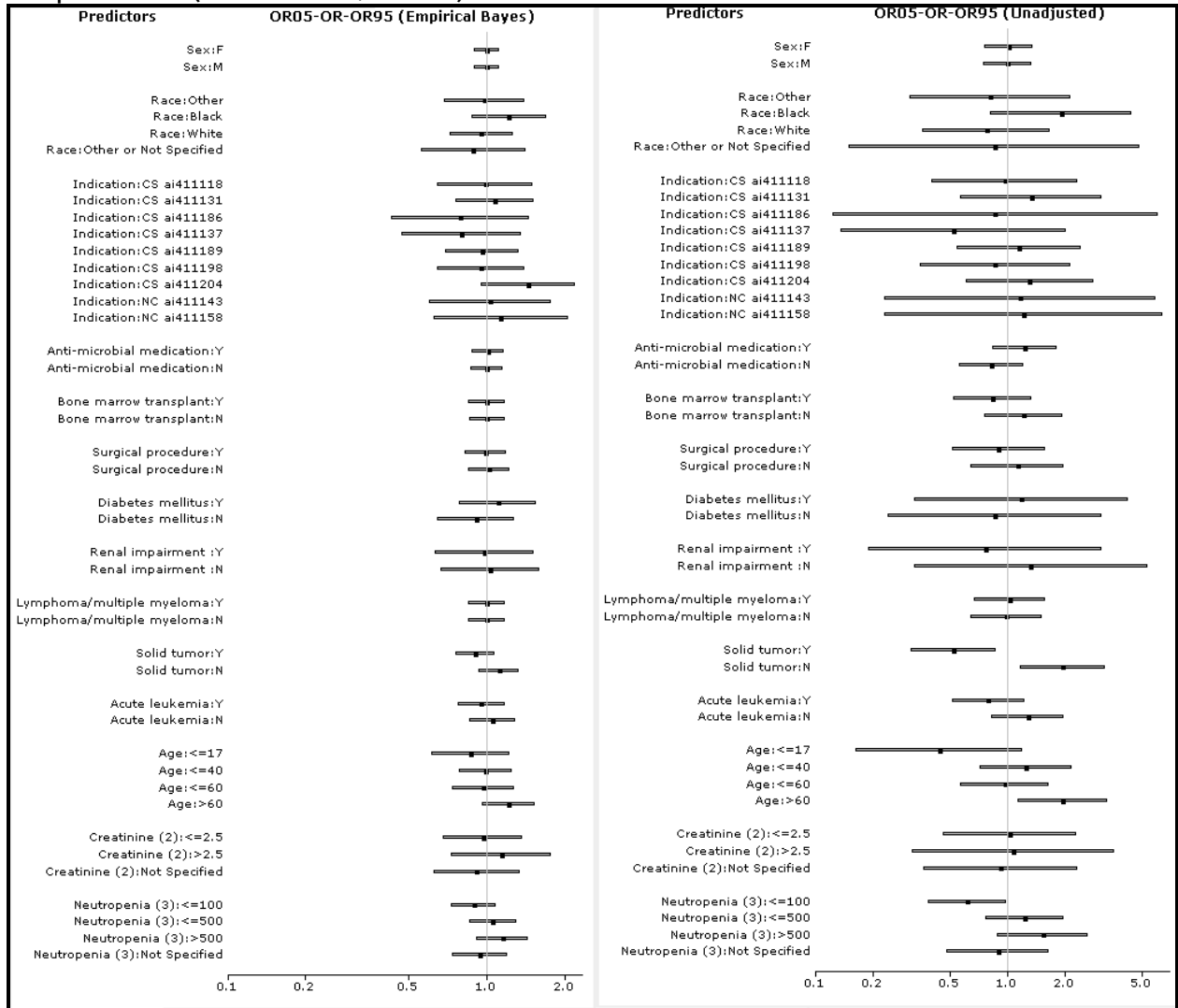
Figure 141: Adjusted (left column) and Unadjusted (right column) Treatment-Comparator Odds Ratios, Overall and for Covariate Subgroups (Issue = 'Death', Run 924)
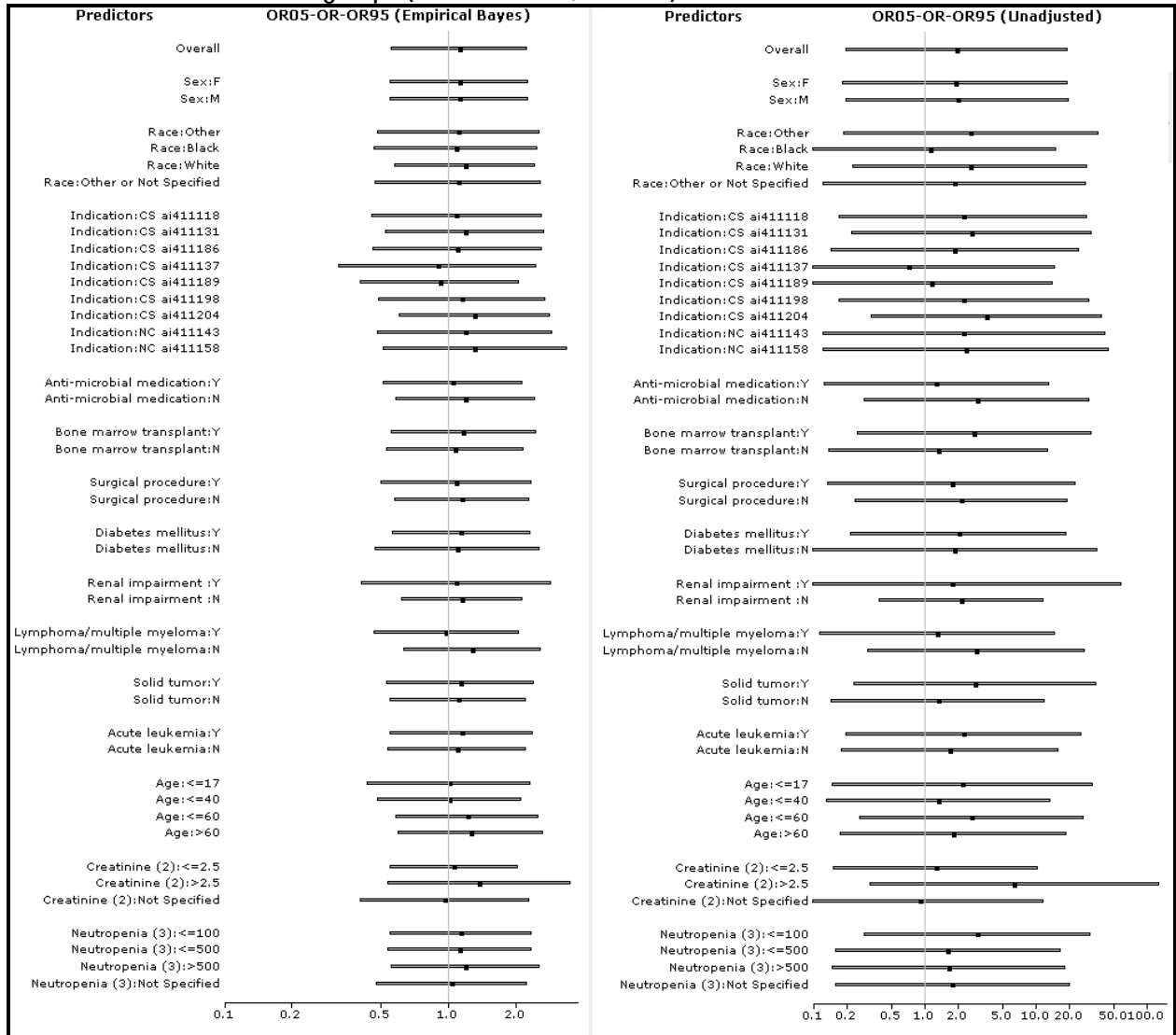
Table 23: Odds Ratios for death by covariate subgroups within the comparator arm (Issue = 'Death', run 924

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Sex:F	0.908	1	1.102	0.769	1.009	1.325	52	620
Sex:M	0.908	1	1.102	0.755	0.991	1.301	62	782
Race:Other	0.696	0.98	1.38	0.316	0.808	2.064	7	92
Race:Black	0.884	1.214	1.668	0.822	1.886	4.323	11	66
Race:White	0.729	0.95	1.238	0.365	0.771	1.629	79	908
Race:Other or Not Specified	0.564	0.883	1.384	0.153	0.852	4.746	17	336
Indication:CS ai411118	0.655	0.982	1.472	0.41	0.963	2.261	9	107
Indication:CS ai411131	0.769	1.071	1.494	0.581	1.32	2.996	15	179
Indication:CS ai411186	0.433	0.787	1.431	0.125	0.857	5.861	17	336

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PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Indication:CS ai411137	0.475	0.797	1.336	0.139	0.522	1.963	1	70
Indication:CS ai411189	0.704	0.957	1.302	0.555	1.143	2.353	18	263
Indication:CS ai411198	0.65	0.946	1.377	0.355	0.859	2.079	8	103
Indication:CS ai411204	0.961	1.436	2.146	0.614	1.298	2.745	34	242
Indication:NC ai411143	0.606	1.028	1.747	0.232	1.151	5.709	8	76
Indication:NC ai411158	0.63	1.132	2.033	0.232	1.199	6.184	4	26
Anti-microbial medication:Y	0.885	1.005	1.141	0.85	1.222	1.756	70	774
Anti-microbial medication:N	0.877	0.995	1.129	0.569	0.818	1.176	44	628
Bone marrow transplant:Y	0.864	0.999	1.155	0.535	0.833	1.297	19	321
Bone marrow transplant:N	0.866	1.001	1.157	0.771	1.201	1.871	95	1081
Surgical procedure:Y	0.832	0.984	1.164	0.522	0.894	1.532	7	61
Surgical procedure:N	0.859	1.016	1.202	0.653	1.118	1.916	107	1341
Diabetes mellitus:Y	0.796	1.103	1.528	0.333	1.169	4.1	97	1066
Diabetes mellitus:N	0.655	0.907	1.256	0.244	0.855	3	17	336
Renal impairment :Y	0.637	0.975	1.493	0.193	0.763	3.023	0	3
Renal impairment :N	0.67	1.025	1.57	0.331	1.31	5.186	114	1399
Lymphoma/multiple myeloma:Y	0.862	1	1.16	0.68	1.017	1.522	30	423
Lymphoma/multiple myeloma:N	0.862	1	1.16	0.657	0.983	1.471	84	979
Solid tumor:Y	0.767	0.901	1.059	0.318	0.521	0.852	23	284
Solid tumor:N	0.944	1.11	1.304	1.173	1.92	3.143	91	1118
Acute leukemia:Y	0.785	0.951	1.153	0.521	0.787	1.19	46	584
Acute leukemia:N	0.867	1.051	1.274	0.84	1.27	1.92	68	818
Age:<=17	0.617	0.861	1.2	0.166	0.439	1.161	4	108
Age:<=40	0.792	0.985	1.226	0.725	1.231	2.092	28	421
Age:<=60	0.748	0.97	1.258	0.578	0.964	1.607	43	571
Age:>60	0.976	1.215	1.513	1.143	1.919	3.223	39	302
Creatinine (2):<=2.5	0.69	0.967	1.354	0.468	1.019	2.216	108	1324
Creatinine (2):>2.5	0.738	1.135	1.747	0.326	1.068	3.497	2	6
Creatinine (2):Not Specified	0.63	0.911	1.317	0.374	0.919	2.257	4	72
Neutropenia (3):<=100	0.741	0.888	1.064	0.392	0.613	0.957	45	687
Neutropenia (3):<=500	0.865	1.05	1.275	0.784	1.221	1.903	35	363
Neutropenia (3):>500	0.921	1.145	1.422	0.891	1.512	2.565	19	145
Neutropenia (3):Not Specified	0.747	0.937	1.176	0.488	0.884	1.603	15	207

Table 24. Treatment-comparator Odds Ratios, overall and by Covariate (Issue = 'Death', run 924)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Overall	0.561	1.11	2.196	0.201	1.918	18.27	73	817
Sex:F	0.553	1.11	2.225	0.189	1.87	18.471	34	374
Sex:M	0.555	1.11	2.218	0.203	1.967	19.01	39	443
Race:Other	0.487	1.101	2.489	0.19	2.57	34.761	5	58
Race:Black	0.471	1.069	2.43	0.088	1.127	14.392	4	31
Race:White	0.579	1.176	2.389	0.234	2.535	27.505	51	499

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Race:Other or Not Specified	0.476	1.095	2.522	0.126	1.842	26.873	13	229
Indication:CS ai411118	0.458	1.08	2.549	0.174	2.203	27.827	5	54
Indication:CS ai411131	0.529	1.176	2.616	0.225	2.6	30.029	9	95
Indication:CS ai411186	0.463	1.089	2.561	0.147	1.851	23.357	13	229
Indication:CS ai411137	0.327	0.89	2.419	0.035	0.704	14.237	0	35
Indication:CS ai411189	0.41	0.909	2.016	0.098	1.149	13.468	8	136
Indication:CS ai411198	0.493	1.143	2.65	0.173	2.236	28.947	5	49
Indication:CS ai411204	0.609	1.301	2.777	0.34	3.561	37.265	21	117
Indication:NC ai411143	0.488	1.178	2.845	0.124	2.219	39.852	8	76
Indication:NC ai411158	0.514	1.301	3.29	0.125	2.311	42.781	4	26
Anti-microbial medication:Y	0.516	1.04	2.095	0.127	1.262	12.582	40	422
Anti-microbial medication:N	0.587	1.184	2.39	0.294	2.913	28.889	33	395
Bone marrow transplant:Y	0.558	1.156	2.396	0.252	2.772	30.453	14	195
Bone marrow transplant:N	0.535	1.065	2.118	0.141	1.326	12.458	59	622
Surgical procedure:Y	0.504	1.077	2.302	0.139	1.748	21.973	4	32
Surgical procedure:N	0.583	1.143	2.241	0.241	2.103	18.359	69	785
Diabetes mellitus:Y	0.568	1.133	2.261	0.223	2.001	17.967	60	588
Diabetes mellitus:N	0.475	1.087	2.485	0.099	1.838	34.1	13	229
Renal impairment :Y	0.414	1.079	2.815	0.054	1.737	55.75	0	2
Renal impairment :N	0.62	1.141	2.101	0.399	2.117	11.223	73	815
Lymphoma/multiple myeloma:Y	0.467	0.969	2.01	0.116	1.282	14.165	14	249
Lymphoma/multiple myeloma:N	0.638	1.271	2.533	0.312	2.869	26.411	59	568
Solid tumor:Y	0.535	1.121	2.35	0.238	2.813	33.241	18	152
Solid tumor:N	0.555	1.099	2.174	0.148	1.307	11.584	55	665
Acute leukemia:Y	0.554	1.135	2.326	0.201	2.213	24.419	32	354
Acute leukemia:N	0.542	1.084	2.171	0.181	1.662	15.25	41	463
Age:<=17	0.44	1.001	2.278	0.152	2.166	30.97	3	57
Age:<=40	0.487	1.005	2.076	0.136	1.332	13.045	17	266
Age:<=60	0.59	1.207	2.468	0.266	2.612	25.686	31	339
Age:>60	0.602	1.249	2.588	0.177	1.794	18.194	22	155
Creatinine (2):<=2.5	0.554	1.053	2.004	0.154	1.242	10.002	69	771
Creatinine (2):>2.5	0.541	1.358	3.406	0.333	6.341	120.863	2	2
Creatinine (2):Not Specified	0.408	0.955	2.236	0.071	0.895	11.211	2	44
Neutropenia (3):<=100	0.554	1.125	2.286	0.29	2.915	29.318	33	401
Neutropenia (3):<=500	0.541	1.113	2.291	0.161	1.605	15.955	21	214
Neutropenia (3):>500	0.557	1.179	2.497	0.153	1.645	17.705	10	81
Neutropenia (3):Not Specified	0.481	1.026	2.191	0.161	1.757	19.141	9	121

4.16.3. *Run 672*

Run 672 only included 3 covariates: study, race, age [3 Covariates: 9 Studies + Age + Race] and 2 Issues: Death + 1 CEF Issue (HCC).

Figure 142: Configuration used with run 672 (included 9 studies)

Configuration options for the selected BLR run:

Dosing

Arm of last randomization {Treatment includes: 'Cefepime', 'Cefepime Plus Vancomycin', 'Ceftazidime Plus Vancomycin-Cefepime Plus Vancomycin', 'Ceftazidime-Cefepime'; Comparator includes: 'Cefepime Plus Vancomycin-Ceftazidime Plus Vancomycin', 'Cefepime-Ceftazidime', 'Ceftazidime', 'Ceftazidime Plus Vancomycin', 'Gentamicin/Piperacillin', 'Mezlocillin/Gentamicin';}

Predictors

Age:
  Age {<=17 <= 17.0; 17.0 < <=40 <= 40.0; 40.0 < <=60 <= 60.0; 60.0 < >60;}

Race:
  Race {Other includes: 'H', 'O', 'X'; Black includes: 'B'; White includes: 'W';}

Issues

PT: Death {MedDRA PT Disproportionality (Death) - from Issue Cluster 'Cluster #34'}
SMQ: Haemorrhagic cerebrovascular conditions [narrow] {Standard MedDRA Query (SMQ) Disproportionality (Haemorrhagic cerebrovascular conditions [narrow])...}

Options

Issues occurring any time

Figure 143: Overall estimates for all the issues in run 672
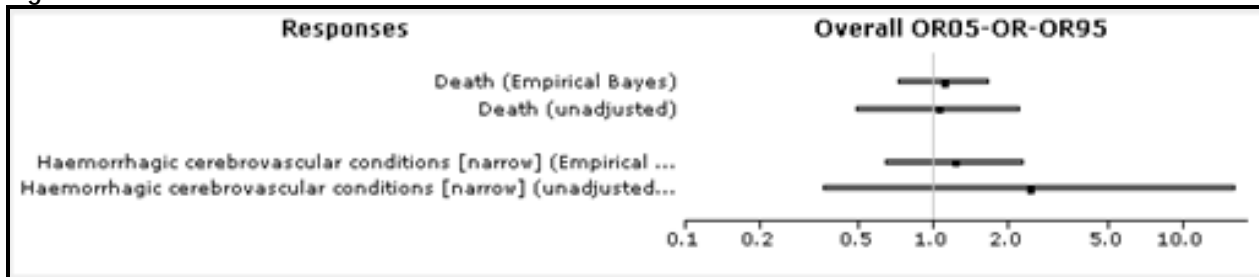
Table 25: Overall estimates for all the issues in run 672

Response	PredictorId	PredictorLabel	BOR05 or OR05	BOR or OR	BOR95 or OR95
Death					
Bayesian	-1	Overall	0.733	1.093	1.63
Unadjusted	-1	Overall	0.501	1.045	2.177
Haemorrhagic cerebrovascular conditions [narrow]					
Bayesian	-1	Overall	0.65	1.203	2.226
Unadjusted	-1	Overall	0.366	2.395	15.665

Figure 144: Adjusted (left column) and Unadjusted (right column) Effects of Covariates Subgroups within the Comparator Arm (Issue = 'Death', Run 672)
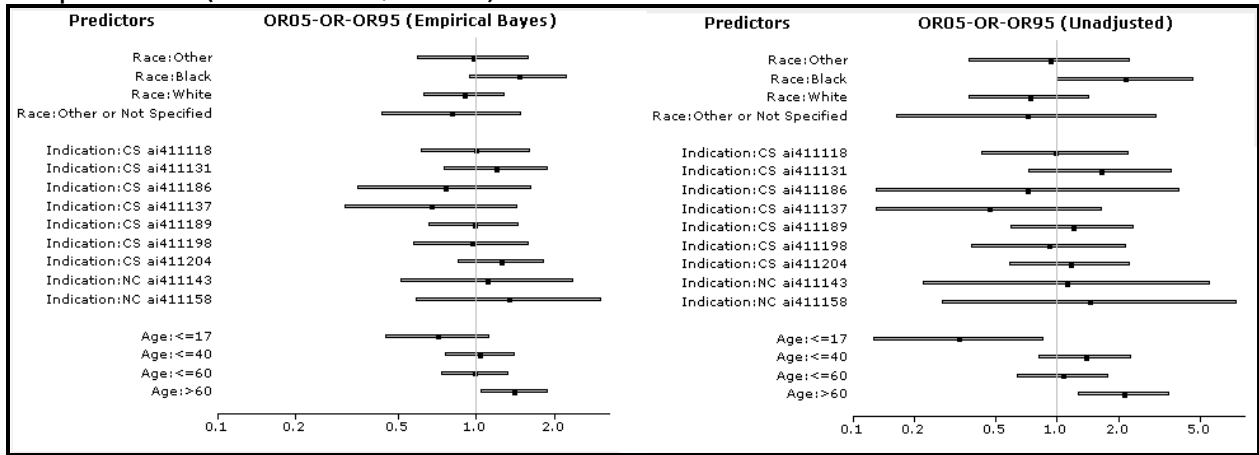
Figure 145: Adjusted (left column) and Unadjusted (right column) Treatment-Comparator Odds Ratios, Overall and for Covariate Subgroups (Issue = 'Death', Run 672)
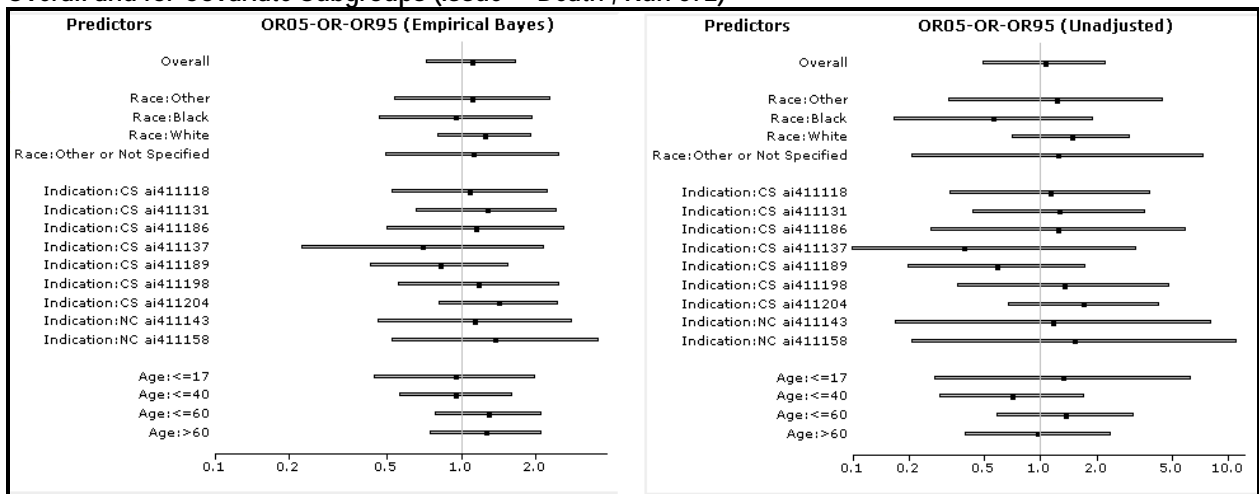
Table 26: Odds Ratios for death by covariate subgroups within the comparator arm (Issue = 'Death', run 672)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Race:Other	0.601	0.969	1.561	0.374	0.913	2.228	7	92
Race:Black	0.951	1.449	2.208	1.002	2.131	4.536	11	66
Race:White	0.632	0.892	1.26	0.378	0.728	1.403	79	908
Race:Other or Not Specified	0.436	0.799	1.467	0.167	0.706	2.977	17	336
Indication:CS ai411118	0.617	0.99	1.587	0.432	0.969	2.175	9	107
Indication:CS ai411131	0.761	1.19	1.862	0.74	1.619	3.54	15	179
Indication:CS ai411186	0.353	0.754	1.61	0.132	0.713	3.854	17	336
Indication:CS ai411137	0.316	0.669	1.414	0.132	0.461	1.609	1	70
Indication:CS ai411189	0.665	0.977	1.436	0.604	1.185	2.327	18	263
Indication:CS ai411198	0.581	0.956	1.574	0.386	0.905	2.125	8	103

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Total Death Occurs (N)	Total Death Not Occurs (N)
Indication:CS ai411204	0.86	1.241	1.791	0.597	1.152	2.221	34	242
Indication:NC ai411143	0.515	1.094	2.324	0.224	1.103	5.422	8	76
Indication:NC ai411158	0.592	1.326	2.968	0.277	1.423	7.31	4	26
Age:<=17	0.452	0.708	1.11	0.128	0.327	0.835	4	108
Age:<=40	0.769	1.029	1.377	0.828	1.367	2.257	28	421
Age:<=60	0.74	0.982	1.303	0.647	1.061	1.74	43	571
Age:>60	1.051	1.395	1.851	1.283	2.111	3.471	39	302

Table 27: Treatment-comparator Odds Ratios, overall and by Covariate (Issue = 'Death', run 672)

PredictorLabel	EBOR05	EBOR	EBOR95	OR05	OR	OR95	Cefepime Death Occurs (N)	Cefepime Death Not Occurs (N)
Overall	0.733	1.093	1.63	0.501	1.045	2.177	73	817
Race:Other	0.544	1.105	2.246	0.329	1.2	4.376	5	58
Race:Black	0.469	0.947	1.916	0.168	0.558	1.847	4	31
Race:White	0.808	1.231	1.876	0.716	1.449	2.936	51	499
Race:Other or Not Specified	0.499	1.107	2.455	0.208	1.228	7.242	13	229
Indication:CS ai411118	0.529	1.078	2.197	0.332	1.11	3.71	5	54
Indication:CS ai411131	0.661	1.26	2.401	0.443	1.247	3.512	9	95
Indication:CS ai411186	0.508	1.14	2.557	0.264	1.234	5.77	13	229
Indication:CS ai411137	0.229	0.695	2.113	0.048	0.388	3.151	0	35
Indication:CS ai411189	0.434	0.813	1.522	0.2	0.582	1.697	8	136
Indication:CS ai411198	0.559	1.17	2.449	0.365	1.316	4.739	5	49
Indication:CS ai411204	0.823	1.415	2.431	0.68	1.684	4.171	21	117
Indication:NC ai411143	0.464	1.129	2.748	0.17	1.158	7.877	8	76
Indication:NC ai411158	0.529	1.363	3.517	0.209	1.495	10.698	4	26
Age:<=17	0.45	0.938	1.957	0.278	1.308	6.154	3	57
Age:<=40	0.567	0.947	1.583	0.297	0.703	1.662	17	266
Age:<=60	0.792	1.285	2.085	0.595	1.349	3.058	31	339
Age:>60	0.754	1.25	2.071	0.401	0.96	2.299	22	155

4.17. How Fast the Review of the Data Went after Reloading the Corrected Data?

After the reviewer switched the baseline and treatment assignment to the most recent episode of FN for the patients with more than one episode of FN the data were loaded into WebSDM CTSD, and **the first MBLR job was completed a few hours later.**

Table 28: Dates of the data loads

Name	Owner	Metadata Format	Oracle Account	Path	Created
Cefepime	Ana Szarfman	Use Standard Metadata	S_CEFEPIME	U:\Data\NDAs\Cefepime\Fdswa150 nonectd N50679 N_000 2008-05-30 \crt\datasets	06/17/2008 10:39:35 EDT
Cefepime 8-29-2008 data	Ana Szarfman	Use Standard Metadata	S_CEFEPIME_8_29_2008_DATA	U:\Data\NDAs\Cefepime\Fdswa150 nonectd N50679N_0002008-08-29 \crt\datasets	09/26/2008 16:19:39 EDT
Cefepime 8-29-2008 data Last Episode	Ana Szarfman	Use Standard Metadata	S_CEFEPIME_8_29_2008_DATA_LA	U:\Data\NDAs\Cefepime\Fdswa150 nonectd N50679N_0002008-08-29 \crt\datasets	02/06/2009 19:27:36 EST

Table 29: Date of the last data load for each study

Indication	Created	Modified
ai411118	02/07/2009 16:44:02 EST	02/09/2009 23:12:01 EST
ai411131	02/07/2009 16:48:17 EST	02/09/2009 23:12:55 EST
ai411186	02/07/2009 16:54:31 EST	02/09/2009 23:13:13 EST
ai411137	02/07/2009 16:56:22 EST	02/09/2009 23:12:31 EST
ai411189	02/09/2009 21:13:39 EST	02/09/2009 23:13:30 EST
ai411204	02/09/2009 21:17:24 EST	02/09/2009 23:14:12 EST
ai411143	02/09/2009 21:20:56 EST	02/09/2009 22:12:15 EST
ai411198	02/09/2009 21:21:59 EST	02/09/2009 23:25:01 EST
ai411158	02/09/2009 21:33:34 EST	02/09/2009 22:21:49 EST

Table 30: Dates of the data pools for the last data load

	Application	ID	Name	Description	Standard	Oracle Account	Created	Modified	State
	Cefepime 8-29-2008 data Last Episode	399	All 9 studies FN LE	<none supplied>	sdm311	S_CEFEPIME_ALL_9_STUDIES_FN_LE	02/09/2009 23:15:13 EST	02/10/2009 16:54:54 EST	Ready to Use
	Cefepime 8-29-2008 data Last Episode	413	All 7 CS FN LE	<none supplied>	sdm311	S__ALL_7_COMPARATIVE_STUDIES_F	02/12/2009 14:22:36 EST	02/13/2009 15:25:56 EST	Ready to Use
	Cefepime 8-29-2008 data Last Episode	414	3 CS Cefepime vs Ceftazidime	<none supplied>	sdm311	S_3_CS_CEFEPIME_VS_CEFTAZIDIME	02/13/2009 15:27:22 EST	02/13/2009 15:31:16 EST	Ready to Use

Table 31: Date of the first MBLR run for the last data load

```
                        Potential Signal Archive
              Potential Signal Name: Death and syndromes
              Audit Version Date: 02/10/2009 23:10:00 EST
                         Last Modifier: ana
          Application: Cefepime 8-29-2008 data Last Episode
                            Description:
                          Assigned To: ana
                            Status: New
              Reason for Status Change: Not Changed
```

4.18.   *Lessons Learned*

4.18.1.   *WebSDM CTSD and MBLR Applied to two Additional NDAs*

The experience of assessing safety data with two additional NDAs was similar to the cefepime experience. The results were obtained in days vs. months, were easily auditable, and consistent with independent assessments and biological plausibility. (20,21)

4.18.2.   *Updated Data Instructions to Sponsors*

The cefepime review experience as well as the experience with 2 additional NDAs helped us prepare updated instructions to sponsors on how to format the clinical data for performing more automated safety analyses, as described in an endnote (22).

4.18.3.   *Need to Update Current Paradigms of Data Submission and Analysis*

With current data submission and review paradigms, it takes longer to transform the data than to analyze the data. With the novel analytical tools that we helped implement, reviewers will have to understand the process of how to select predictors and how to adjust by predictor.

The reviewers will not have the need to understand or write programming code for the majority of their analyses. Instead of manually changing the programming codes, the programs are run automatically, giving the reviewers more time to assess and interpret the results and communicate with each other in front of the same data.

To take full advantage of the new automated methods capable of using standardized subject level data, we need to actively work to generate comprehensive data standards for CT data.

These new methods improve the overall access to the data and organize the results into a standardized format that facilitates interpretation. These tools have shown to have a broad practical impact of increased productivity.

These analytical tools not only help find gaps in the data standards, but also gaps in the data collection. For example, we could not analyze the effect that the most recent neutrophil count could have on the death effect because the sponsor stopped collecting data after EOT (See Figure 36). This important gap in the data collection would not be easily identified by using line listings of the data or by generating thousands of 2x2 non-integrated outputs.

The MBLR as well as any other result in WebSDM CTSD are automatically hyperlinked to other representations of the data, including to Patient Profile displays. These functions give the reviewers a deeper understanding of the complex, multivariate data analyzed. These functions increase the ability of the reviewer to identify and document data issues that require correction, to make (or to request informed data corrections), and to rerun the MBLR results with updated and corrected information, all in real time.

Instead of trying to guess which data the reviewer will need to process before analysis, the MBLR method starts with a comprehensive set of data in CDISC format, and uses automation to generate comprehensive analyses of the data, enabling the reviewer to interpret the results by drilling down to the data behind the results.

The time spent in trying to transform data that may not be critical or sufficient to complete an analysis, is instead spent in understanding which predictors and issues to select.

The review of cefepime required an iterative process. The process included the identification and correction of gaps in the data and in the evolving SDTM CDISC standards, the visualization of the integrated data and confirmation that the data transformation was correct, and the generation and visualization of the MBLR results. Some of the major gaps that we identified and corrected included a lack of a unique place for deaths in the data standards, of a consistent representation of exposure, and of a unique representation of multiple episodes of treatment.

SDTM CDISC still does not support a unique standardized place for recording the patients who died and the death details, including date of death typically collected with a mortality report. This experience is the crux of the argument forwarded to the CDISC implementation committee to create a unique place for "deaths" in the next version of SDTM.

Without automated analytical tools and hands-on testing the soundness of the data standards as they evolve and mature, the process of refining the data standards for CT data, which is of prime importance to access the data in a timely manner, will take longer than needed.

The cost of implementation of these analytical tools was a bargain at $19,600 and ½ of an FTE of a Medical Officer with experience in implementing novel analytical tools.

The Agency can expect an increase in publications/citizen petitions based on meta-analyses of public domain CT results. It is also often necessary to reanalyze CT data in light of new information about a particular adverse event or class of events for a drug or class of drugs months—or even years—after the initial analysis. With current ad-hoc methods, the prevalent use of non-standardized data and lack of automated review tools, the process of re-evaluation may take as long to perform as the original review.(5)

Another advantage, with the new methodology that this reviewer used to perform the cefepime review: the results are easier and quicker to obtain and easier to audit by other reviewers. (See Section 4.17).

4.19. *General Information about Safety Data Mining of CT Data*

4.19.1. *Clinical Trial Data*

- High-quality treatment and control data consistently collected according to a defined protocol

- Good identification of study drug names and major events

- Laboratory values (elevated liver enzymes) and other adverse event precursor data available

4.19.1.1. *Limitations of Clinical Trials*

- CTs are inherently too short, with study populations that are too small and too homogeneous to detect important but relatively rare adverse events in the general population

- Studies are not generally powered to assess safety endpoints

- Patient randomization may not always be effective in eliminating bias. For example, it is very difficult to randomize when it is unknown if the pathogen being treated will be sensitive to the drug treatment or studies with multiple episodes of FN

- Relatively small total numbers of patients

- Not often included enough patients in important subgroups (pediatric, elderly, women, renal failure)

- Little data or not data on long-term exposure; little long-term follow-up

- High costs and long time periods before results are available

- No common use of a common standardized data structure and nomenclature

- Data standards for CT data are just emerging

- Not a good identification of concomitant medications, medical history

- Coding errors and misspellings

- Incorrect coding (missing fields, indications entered as adverse events, etc.)

- Information may not be coded properly (note the multiple representations of Acute leukemia in this review)

- Potential for not monitoring potential safety issues of importance, not known a priori

- No certainty that a reported event is causal

- Inconsistent data practices across studies that complicates the re-analysis of the data and the auditing of the analytical processes

4.19.2. *Data Mining of Clinical Trials*

- *Method implemented at the FDA:* a Multivariate Bayesian Logistic Regression method named MBLR

- Goal of Data Mining of CT data at the FDA: to detect ***stable safety signals*** in CT data.

- *Impact:* once meaningful patterns are identified, information can be evaluated across other safety databases, as appropriate.

4.19.2.1. *What Opportunities Does MBLR Provide?*

- Even when specific questions are not asked MBLR provides stable safety signals adjusted for multiplicity and small counts

- Provides potential clues to complex safety issues quickly

- Signals important information that might be missed if the question is not asked

4.19.3. *What is MBLR?*

Is a Bayesian Logistic Regression for Subgroup Analyses of Multiple Events (9)

Starts from a set of *Medically Related* events to study

- Set of events from potential signal

- Set of events from SOR clusters (potential syndromes

- Set of ad-hoc events, or all events within a MedDRA SOC

Fits Logistic Regressions to each AE as a response

- Uses exactly the same predictor model for each AE

- Age, gender, concomitant medication, medical history, etc.

- Includes treatment and interactions with treatment as predictors

- Generates parameter estimates for predictors and interactions

Performs Empirical Bayes shrinkage of estimated coefficients

- Coefficients of each predictor borrow strength across AEs

- Overall treatment and interaction effects shrink toward 0

Displays Subgroup Effects

- Bayesian Logistic Regression Coefficients Are Interpreted as Logs of Odds Ratios

- Graphs of confidence intervals for each subgroup

- Confidence intervals that do not overlap are interpreted as significant differences in subgroups

Produces separate graph for each covariate and AE

- Different layouts possible

- Compares original and shrinkage estimates

- Compares overall treatment effects across AEs

- Compares subgroup effects across medically related AEs

4.19.3.1.1. *Limitations of MBLR*

The absence of a "signal" does not rule out a safety problem.

5. Notes and References

1 Paul M, Yahav D, Fraser A, Leibovici L. Empirical antibiotic monotherapy for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. J Antimicrob Chemother. 2006 Feb;57(2):176-89.

2 Yahav D, Paul M, Fraser A, Sarid N, Leibovici L. Efficacy and safety of Cefepime: a systematic review and meta-analysis. Lancet Infect Dis. 2007 May;7(5):338-48.

3 Wittes J. On looking at subgroups. Circulation. 2009 Feb 24;119(7):912-5.

4 Study ai111204 included in the Yahav, Paul, et al paper as Chandrasekar 2000 had a total of 143 cefepime patients and 133 comparator patients as in the randomized treatments for the first episode of FN, whereas Study ai111204 had 138 patients each in the last episode of FN.

5 Szarfman A. Levine JG, Tonning JM. Chapter 27. A New Paradigm for Analyzing Adverse Drug Events. In: Computer Applications in Pharmaceutical Research and Development. Edited by Sean Ekins, Published by John Wiley and Sons. 2006.

Szarfman A. Levine JG, Tonning JM. Chapter 9.8. A New Paradigm for Analyzing Adverse Drug Events. In: Clinical Trials Handbook, by Shayne Cox Gad. Published by John Wiley and Sons, Inc. 2009.

6 Adapted from the documentation of the CTSD WebSDM software package

7 WebSDM (Web Submission Data Manager) started to be implemented under a Cooperative Research and Development Agreement (CRADA) between the FDA and Lincoln Technologies, Phase Forward's safety division in the Spring of 2002.

WebSDM© with Clinical Trials Signal Detection™ (CTSD). WebSDM (Web Submission Data Manager) is a web-based system that is designed to work with clinical trial data submitted to the Food and Drug Administration (FDA) consistent with the CDISC electronic submission data standards. (CDISC is the Clinical Data Interchange Standards Consortium.)

WebSDM enables to:

Verify that the case report provided data conform to the CDISC Study Data Tabulation Model (SDTM). The checking process checks the metadata and clinical data for compliance with CDISC standards; some checks are built-in and some are added as rules (edit checks) by users with appropriate permissions.

View summary and detailed clinical data and metadata for domains in practical formats for review and export.

Query the study data by specifying variable-based criteria and save lists of subjects meeting those criteria.

Define and run summary and detail reports based on study data.

Basic workflow in CTSD

After an application and study (or studies) are registered, the study data is loaded and checked, which makes the clinical data, metadata, and any identified structure or consistency errors available for review on the Domains tab. During review, the data can be downloaded to third-party applications for further review and analysis. Reviewers can also create lists of subjects based on specified criteria and then produce reports or view graphs in WebSDM. Options to use PPD Patient Profiles® or Stottler Henke DataMontage to view graphical representations of data are also available if appropriate prerequisites are met.

The following diagram shows the basic workflow for working with domain data in WebSDM. Tasks with a blue background are performed by users responsible for loading studies, and tasks with a green background are performed by medical and statistical reviewers.
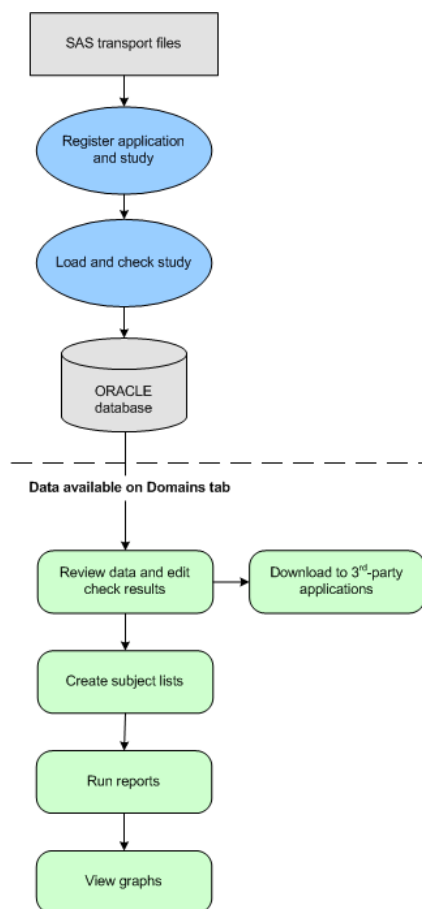
8 Study Data Tabulation Model (SDTM) of the Clinical Data Interchange Standards Consortium (CDISC) <http://www.cdisc.org/index.html>

The datasets submitted by the applicant did not make use of CDISC controlled terminology (that is the standard codelists CDISC has defined). Some of the analyses in CTSD, like examining study dropouts, depend on use of controlled terminology. While this was not especially important for this study, in terms of methodology it could be more important in the future.

9 DuMouchel describes the novel statistical methodology included in this review in the program documentation and/or help messages, and clarified issues during several presentations at the FDA on October 29, 2008 and on March 16, 2009, and during numerous conversations with this reviewer, and other scientists at the FDA including Drs. Joy Mele and Ram Tiwari.

10 Figures of ORs use a logarithmic scale. The reader should pay attention to the scales to understand the magnitude of the cefepime effects, with much wider estimates for the unadjusted values.

11 The Center Director provided funds to support the "Loading and Analysis of 9 SDTM clinical trials using CTSD and the incorporation of a re-usable R-based module to perform

'Meta-Analysis of Complete Subject Level Data from Clinical Trials' submitted in CDISC format, with Ana Szarfman as the Principal Investigator. William DuMouchel developed the MBLR methodology for this project. The contract #1047767, awarded on September 18 2008, was for a total of $19,600.

12 Instructions sent to BMS regarding the transformation of the Cefepime data into SDTM CDISC standards:

We plan to expedite a careful re-evaluation of the conclusions for FN in the meta-analysis by Yahav et al by using processes that will facilitate the access and integration of the Sponsor's raw clinical trial data collected for the all Cefepime clinical trials that studied FN (including both those submitted to the US and the so called "Unpublished Studies"):

1.   Comparative trials submitted to the US:

   a.   AI411-131
   b.   AI411-189
   c.   AI411-204
   d.   AI411-118
   e.   AI411-137
   f.   AI411-186
   g.   AI411-198

2.   Non-comparative trials submitted to the US:

   a.   AI411-143
   b.   AI411-158
   3.   "Unpublished Studies"
   a.   AI411-242
   b.   CPM079801
   c.   CPM229502
   d.   CPM239302
   e.   CPM619401
   f.   CPM619513
   g.   CPM679602
   h.   AI4116002
   i.   CPM229305

Please plan to load, integrate, and validate the SDTM SDISC formatted clinical trial data collected for all the Cefepime FN studies listed above before submission to the FDA. We plan to use a standard submission review tool to load and pool the validated data and integrated analytical tools to simplify the re-assessment of the Cefepime data.

I. Please format the following datasets (domains) in the current version of CDISC/Study Data Tabulation Model (SDTM) version 1.1, SDTM Implementation Guide (SDTMIG) version 3.1.1.

   Demographics = DM
   Concomitant medications = CM
   Exposure = EX
   Adverse events = AE

Use the same version of MedDRA across all trials.
Disposition = DS
Medical history = MH
Laboratory tests = LB

We are specifically interested in the following laboratory tests values

Serum chemistry: creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, and alkaline phosphatase

Hematology: White blood cell count and absolute neutrophil count

II. Please create a Procedure dataset following the CM format described above.

We are specifically interested in bone marrow and organ transplant, dialysis, and autopsy report.

III. Format the following datasets (domains) using SDTMIG version 3.1.2.

Microbiology = MB
Microbiology susceptibility = MS
Pharmacokinetics Concentrations = PC
Pharmacokinetics Parameters = PP

IV. Please provide a text file that describes the indication of treatment, as follows:

The first variable of such a text file should contain the USUBJID. The second variable should contain the text of the indication. The third variable should contain a more comprehensive description of the indication and the criteria followed for evaluating the indication.

The three variables should be separated by a tab. The description text should not contain tabs or hard returns.

The first row should contain information for the first patient

The second row for the second patient, etc

The following is a template format (see attachment):

USUBJID	Indication	Description
01019929944	CAP	Resolution of clinical signs and symptoms xxxxxxxxxxxxxxxx

01888777666	CUTI	Resolution of clinical signs and symptoms xxxxxxxxxxxxxxx

V. Please provide a text file with the integrated narrative for each patient who developed serious adverse event(s), withdrew due to an adverse event, and/or died. Please include the outcomes of every serious adverse event, including, but not limited to withdrawals and fatalities. Include all associated Causes of Death.

The first field of such a text file should contain the USUBJID. The second field should contain the text of the narrative. The USUBJID field and the narrative fields should be separated by a tab. The narrative text should contain information for all serious events, outcomes for serious adverse events, withdrawals, and deaths integrated into a single narrative text. The narrative text should not contain tabs or hard returns.

The first row should contain information for the first patient

The second row for the second patient, etc.

The following is a template format (see attachment):

USUBJID	Narrative
01019929944	xxxxxxxxxxxxxxxxxxxx
01888777666	xxxxxxxxxxxxxxxxxxxx

VII. Additional Notes:

Please provide lab data using uniform units of measurement across all the trials.

Please follow the same character format for the USUBJID across all the trials and datasets, including narratives and indication text files.

Please follow the same CDISC format for dates across all the trials and datasets.

Please provide electronic copies of all protocols and protocol amendments.

13 CDISC/Study Data Tabulation Model (SDTM) version 1.1, SDTM Implementation Guide (SDTMIG) version 3.1.1.

14 CTSD Version 2.6, Build 957 and 959.

15 SDTM-compliant variables that capture values for which there are no standard variables in the general observation classes.

16 From the CTSD software:

Shrunken odds ratio statistic as: A'D'/B'C'where:

A' = A+1
B' = B + (B+D)/(A+C)
C' = C + (C+D)/(A+B)
D' = D + [(B+D)(C+D)]/[(A+C)(A+B)]
The logic behind this definition may be understood as follows. A table of A', B', C', and D' is formed by pooling the original table (A, B, C, D) with a prior distribution table (A", B", C", D") where:
A" = 1
B" = (B+D)/(A+C)
C" = (C+D)/(A+B)
D" = B"C" = [(B+D)(C+D)]/[(A+C)(A+B)]
The values A", B", C", D" are the values that satisfy the following constraints:
Constraint
Meaning
A" = 1
 1 is added to the count of subjects who received the study treatment and experienced the issue.
 (A"+B")/(C"+D") = (A+B)/(C+D)
 The ratio of treatment subjects to control subjects is preserved.
 (A"+C")/(B"+D") = (A+C)/(B+D)
 The ratio of subjects with the issue to subjects without the issue is preserved.
A"D" = B"C"
 The odds ratio is 1, thus shrinking towards the independence model.

17 Szarfman A, Talarico L, Levine JG. Chapter 4.21. Analysis and Risk Assessment of Hematological Data from Clinical Trials. In Volume 4, Toxicology of the Hematopoietic System, In: Comprehensive Toxicology. 4:363-79,1997. Editors-in-chief: I.Glenn Sipes, Charlene A.McQueen, A. Jay Gandolfi. Elsevier Science Inc.

18 Charles Joseph Minard's portrait of the losses suffered by Napoleon's army in the Russian campaign of 1812. see http://www.edwardtufte.com/tufte/posters

19 Discussion with Dr. Fred Sorbello

20 JANUS project: Lovenox NDA 22-138 NDA for the Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), presentation to the applicant of May 15, 2009

21 Supplemental new drug application (sNDA) 20-850/S-025, telmisartan tablets, 80 milligrams (mg), Boehringer Ingelheim Pharmaceuticals, Inc., for the proposed indication of reduction in the risk of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for congestive heart failure in patients 55 years or older who are at high risk of developing major cardiovascular events. Cardiovascular and Renal Drugs Advisory Committee Meeting of July 29, 2009

22 DCRP requests for formatting the clinical data for performing a Medical Officer's review of safety data of an NDA

(These guidelines do NOT necessarily apply to other review divisions)

We hope to use a standard submission review tool to load, validate, and pool your data. The tool requires data in SDTM CDISC format. We plan to use these integrated, centrally programmed analytical tools to simplify and speed the review.

We hope to use a standard submission review tool to load, validate, and pool your data. The tool requires data in SDTM CDISC format. We plan to use these integrated, centrally programmed analytical tools to simplify and speed the review.

I. SDTM data:

Format the datasets in the current version of CDISC/Study Data Tabulation Model (SDTM) version 1.2, SDTM Implementation Guide (SDTMIG) version 3.1.2.

Please load, integrate, and validate the SDTM CDISC formatted clinical trial data for all the studies before submission to the FDA, and use these files to review the safety data prior submission.

USUBJID: Follow the same character format for the USUBJID across all the trials and datasets, including narratives. Do not add leading or trailing spaces in any dataset

Dates: Follow the same CDISC format for dates across all the trials and datasets.

Laboratory data and other measurements: Provide these data using common, uniform units of measurements across all trials, as well as the original values in the CRFs.

Adverse events: Provide Adverse Event data using the same version of MedDRA across all trials, as well as the original terms in the CRFs.

Drug names: Provide the drug names for concomitant medications using a common dictionary across all trials, as well as the original terms in the CRFs.

Procedures: Provide the names of procedures using a common dictionary across all trials, as well as the original terms in the CRFs.

Indications: Provide the indications for drugs and procedures using a common dictionary across all trials, as well as the original terms in the CRFs.

Concomitant conditions: Provide concomitant conditions terms using a common dictionary, as well as the original terms in the CRFs.

Medical history: Provide medical history terms using a common dictionary, as well as the original terms in the CRFs.

Exposure: Provide the exposure data in a consistent format across all the studies ("one record" per dose per day).

Deaths: The current SDTM version 3.1.2 does not address the need for a unique place for recording deaths. SDTM CDISC still contains several different places to record deaths.

To simplify our safety analysis, for each patient who died there should be one record in the Disposition domain where DSCAT='DISPOSITION EVENT' and DSDECOD='DEATH'. When there is more than one disposition event the EPOCH variable should be used to distinguish between them so that if the death occurred during the treatment period EPOCH='TREATMENT' and if the death occurred during the follow-up period EPOCH='FOLLOW-UP'. Other values may be used for epoch depending upon the terminology used in the trial design model datasets.

Comments: The tools that we plan to use, work with SDTM data, not with ADaM data.

We prefer that you also include all the derived data used in your analyses in SDTM submissions, including:

Baseline flags for Laboratory results, Vital Signs, ECG, Pharmacokinetic, Microbiology results

EPOCH designators for studies that are not a straight parallel design

STDY variables in SE or other findings domains

Exposure – total dose

II. Narratives:

A patient narrative is a computer readable textual description of the patient's events and patient's care.

The narrative text should integrate the information on all serious events, outcomes of serious adverse events, withdrawals, deaths, and Causes of Death, autopsy reports, concomitant conditions and procedures, etc. into a single narrative text. The narrative text should describe the patient's disease and event progression and patient's care.

File format: Narrative data should be submitted as plain ASCII text (txt) files. Each row of the file has two fields delimited by tab characters.

The first field is the unique subject ID (USUBJID) that is used in the submission. Because the USUBJID will be used to link the narratives to other data in the submission, the USUBJID should be identical to the USUBJID used in all other submission data sets, such as the SDTM datasets.

The second field is the text of the narrative. The narrative must not contain TABS, HARD RETURNS, non-printing characters, or hidden "funny" or formatted characters.

Naming narrative files: The file should be named narrative.txt.

It helps the process of preparation of the narrative text files, if these files are checked for the presence of only two fields: the first one with only the USUBJID (with the right character length), and the second one with only the "long" or "clob" field.

Narrative template format:

USUBJID	Narrative
01019929944	Patient made full recovery, and has no residual pain
01888777666	Patient is still hospitalized in ICU
Etc.	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-50679	GI-1	BRISTOL MYERS SQUIBB CO PHARMACEUTICA L RESEARCH INSTITUTE	MAXIPIME

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/s/

ANA SZARFMAN

12/04/2009

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