Early Sedation with Dexmedetomidine in Ventilated Critically Ill Patients

Heterogeneity of Treatment Effect in the SPICE III Trial

Supplementary Information

Contents

1. E-METHODS

1.1. CLUSTERING PROCESS

For cluster detection, based on clinical relevance, the following variables were selected a priori: 1) Acute Physiology and Chronic Health Evaluation (APACHE) II [1] without the age component; 2) baseline PaO2 / FiO2 ratio; 3) admission diagnosis (defined in mutually exclusive categories as sepsis, respiratory, gastrointestinal, cardiovascular, trauma, neurological or other); 4) type of admission (defined as medical, elective surgery or emergency surgery); 5) ICU source of admission (defined in mutually exclusive categories as emergency department, ward, transferred from other services or operating room); 6) gender (male or female); 7) baseline use of opioids (morphine or fentanyl); 8) baseline use of propofol; 9) baseline use of midazolam; 10) baseline use of ketamine; and 11) baseline use of dexmedetomidine.

Age was not considered in the cluster process to allow the check of interaction between clusters and age.

We used the K–means for mixed large data (kamila) method to detect the clusters. The best number of clusters was defined by inspecting the prediction strength of clusters after 1,000 cross–validations [2, 3]. In addition, we performed a visual display of such clustering method using the Barnes–Hut t–distributed Stochastic Neighbor Embedding (tSNE) method with Gower's distance clustering to confirm and visually display the results and the average silhouette method with Partitioning Around Medoids (PAM) algorithm to confirm and visually display the optimal number of clusters [4].

1.1. Statistical analysis

All hierarchical models were modelled as a simple regression and shrinkage model. The hierarchical models partially pool the data and shrink the estimates in each subgroup towards the overall estimate, with shrinkage proportional to the size of the subgroup. While traditional

subgroup analyses are at higher risk of increased type 1 error due to exaggeration of the subgroup effects, the proposed hierarchical model limits this risk through shrinkage.

All described Bayesian models were done using a Markov Chain Monte Carlo simulation with four chains. All models considered a burn–in of 1,000 iterations, with sampling from a further 10,000 iterations for each chain. All chains were required to be free of divergent transitions and additional sampler settings (adapt_delta) were tuned accordingly until this was achieved. To monitor convergence, trace plots, and the Gelman–Rubin convergence diagnostic (Rhat < 1.01) were used for all parameters. All final models were adequate according to all these diagnostic checks.

1.1. Priors

For all analysis, weakly informative priors were used, aiming to encompass all plausible effect sizes. Since the sample size of the original study is large, it was expected that the likelihood would dominate the posteriors. The priors on treatment effect were based on the most recent meta-analysis on the effect of sedation with dexmedetomidine against usual care in general ICU patients [5]. The SPICE III trial was not included in the updated version. According to this data, the effect estimate of dexmedetomidine on mortality (after converting risk ratio to odds ratio [OR]) is 1.00 (0.82 to 1.21), according to 16 studies with 1994 patients [5]. To account for potential bias in previous studies and also differences in population, control arm and intervention, wide priors were considered, and the priors were centred on null (OR = 1.00) to reflect the clinical equipoise.

The following priors were used for 90-day mortality outcome:

- Intercept: normally distributed prior with mean 0 and variance 2.25 (prior risk with a 95% probability between 5% and 95%);
- Treatment effect: normally distributed prior with mean 0 and variance of 0.25 (corresponding to an OR of 1.00 with 95% prior probability of an OR among 0.37 to 2.66);

- Shrinkage parameter: normally distributed prior with mean of 0 and variance of Ω, where Ω is the shrinkage factor having a half-normally distributed prior with variance of 1; and
- Age and interaction age x group in the continuous scale (Figure 2): normally distributed prior with mean 0 and variance 0.01 for both terms (corresponding to an OR with mean of 1.00 with 95% prior probability of an OR among 0.82 to 1.22 for a 1-point increase in APACHE II).

There is no pooled information on the effect of dexmedetomidine in the specific outcome of coma and delirium free days or ventilator-free days in general ICU patients compared to usual care. Thus, we arbitrarily selected wide priors centered on null (mean difference [MD] = 0.00), similar to the priors used for the primary outcome, to also reflect the clinical equipoise.

- Intercept: normally distributed prior with mean 0 and variance 2.25 (prior risk with a 95% probability between 5% and 95%);
- Treatment effect: normally distributed prior with mean 0 and variance of 0.25 (corresponding to an MD of 0.00 with 95% prior probability of an MD among -0.98 to 0.98);
- Shrinkage parameter: normally distributed prior with mean of 0 and variance of Ω, where Ω is the shrinkage factor having a half-normally distributed prior with variance of 1;
- Age and interaction age x group in the continuous scale (Figure 2): normally distributed prior with mean 0 and variance 0.01 for both terms (corresponding to an MD with mean of 0.00 with 95% prior probability of an MD among -0.196 to 0.196 for a 1-point increase in APACHE II).

For the additional interaction analyses, the following weakly informative priors were considered (Figure 4 and 5):

- Intercept: normally distributed prior with mean 0 and variance 2.25 (prior risk with a 95% probability between 5% and 95%);
- Treatment effect: normally distributed prior with mean 0 and variance of 0.25 (corresponding to an OR of 1.00 with 95% prior probability of an OR among 0.37 to 2.66);
- Age category and APACHE II (Figure 4), and cluster and age (Figure 5): normally distributed prior with mean 0 and variance 0.01 (corresponding to an OR with mean of 1.00 with 95% prior probability of an OR among 0.82 to 1.22).

1.2. Sensitivity analyses

1.2.1. Pessimistic priors

Priors corresponding to prior belief that early use of dexmedetomidine is associated with increase in 90-day mortality and decrease in coma and delirium free days, respectively (all other priors were the same as described above):

- Treatment effect: normally distributed prior with mean 0.15 and variance of 0.25 (corresponding to an OR of 1.16 with 95% prior probability of an OR among 0.44 to 3.09); or
- Treatment effect: normally distributed prior with mean -0.50 and variance of 0.25 (corresponding to an MD of -0.50 with 95% prior probability of an MD among -1.48 to 0.48).

1.2.2. Optimistic priors

Priors corresponding to prior belief that early use of dexmedetomidine is associated with decrease in 90-day mortality and increase in coma and delirium free days, respectively (all other priors were the same as described above):

- Treatment effect: normally distributed prior with mean -0.15 and variance of 0.25 (corresponding to an OR of 0.86 with 95% prior probability of an OR among 0.32 to 2.29); or
- Treatment effect: normally distributed prior with mean 0.50 and variance of 0.25 (corresponding to an MD of 0.50 with 95% prior probability of an MD among -0.48 to 1.48).

2. E-TABLES

2.1. E-TABLE 1: RATE OF MISSING VALUES IN VARIABLES OF INTEREST

	Total	Age > 65 years (*n* = 1825)	Age ≤ 65 years (*n* = 2079)	Cluster 1 (*n* = 976)	Cluster 2 (*n* = 2346)
Age	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gender	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight	2 (0.1)	1 (0.1)	1 (0.0)	0 (0.0)	1 (0.0)
APACHE II	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Time until randomization	29 (0.7)	13 (0.7)	16 (0.8)	4 (0.4)	11 (0.5)
Allocation group	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes treated with insulin	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Type of admission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Admission diagnosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ICU source of admission	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PaO_2 / FiO_2*	421 (10.8)	186 (10.2)	235 (11.3)	0 (0.0)	0 (0.0)
Baseline use of opioids*,[a]	206 (5.3)	88 (4.8)	118 (5.7)	0 (0.0)	0 (0.0)
Baseline use of propofol*	206 (5.3)	88 (4.8)	118 (5.7)	0 (0.0)	0 (0.0)
Baseline use of midazolam*	206 (5.3)	88 (4.8)	118 (5.7)	0 (0.0)	0 (0.0)
Baseline use of ketamine*	206 (5.3)	88 (4.8)	118 (5.7)	0 (0.0)	0 (0.0)
Baseline use of dexmedetomidine*	206 (5.3)	88 (4.8)	118 (5.7)	0 (0.0)	0 (0.0)
90-day mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Coma and delirium free days	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventilator-free days	16 (0.4)	3 (0.2)	13 (0.6)	4 (0.4)	11 (0.5)

Data are N (%). *APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit*

Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients

* Patients with missing data in these variables were excluded from the clustering process

[a] Opioids aggregate the use of morphine and/or fentanyl

2.2. E-TABLE 2: SENSITIVITY ANALYSIS FOR THE CLUSTERING PROCESS

	Original Cohort (*n* = 3322)			Without Baseline Sedation Variables (*n* = 3483)			Without Baseline Sedation Variables and with PaO_2 / FiO_2 Imputed by the Median (*n* = 3904)		
	Cluster 1 (*n* = 976)	**Cluster 2 (*n* = 2346)**	***p* value**	**Cluster 1 (*n* = 1006)**	**Cluster 2 (*n* = 2477)**	***p* value**	**Cluster 1 (*n* = 1139)**	**Cluster 2 (*n* = 2765)**	***p* value**
Age, years	64.7 (53.2 – 74.1)	63.6 (52.2 – 72.6)	0.038	64.7 (53.0 – 74.4)	63.6 (52.2 – 72.6)	0.027	64.0 (51.5 – 73.9)	63.7 (52.4 – 72.5)	0.358
Female gender – no (%)*	334 (34.2)	927 (39.5)	0.004	347 (34.5)	986 (39.8)	0.003	393 (34.5)	1102 (39.9)	0.002
Weight, kg	81.0 (70.0 – 97.0)	78.0 (65.0 – 93.0)	< 0.001	81.0 (70.0 – 97.0)	78.0 (65.0 – 93.0)	< 0.001	81.0 (70.0 – 97.0)	79.0 (65.0 – 93.0)	< 0.001
APACHE II	19.0 (15.0 – 24.0)	23.0 (18.0 – 29.0)	< 0.001	19.0 (15.0 – 24.0)	23.0 (18.0 – 29.0)	< 0.001	19.0 (14.0 – 23.0)	23.0 (18.0 – 28.0)	< 0.001
Without age*	15.0 (11.0 – 20.0)	19.0 (15.0 – 25.0)	< 0.001	15.0 (11.0 – 20.0)	19.0 (15.0 – 25.0)	< 0.001	15.0 (11.0 – 19.5)	19.0 (14.0 – 24.0)	< 0.001
Time to randomization, hours	5.5 (2.5 – 9.6)	4.5 (2.0 – 8.5)	< 0.001	5.4 (2.4 – 9.4)	4.3 (1.8 – 8.3)	< 0.001	5.5 (2.3 – 9.6)	4.2 (1.7 – 8.3)	< 0.001
Dexmedetomidine group – no (%)	488 (50.0)	1165 (49.7)	0.879	500 (49.7)	1229 (49.6)	0.970	567 (49.8)	1381 (49.9)	0.944
Diabetes with insulin – no (%)	61 (6.2)	246 (10.5)	< 0.001	61 (6.1)	255 (10.3)	< 0.001	80 (7.0)	310 (11.2)	< 0.001
Type of admission – no (%)*			< 0.001			< 0.001			< 0.001
Non-operative	11 (1.1)	2343 (99.9)		12 (1.2)	2477 (100.0)		14 (1.2)	2765 (100.0)	
Elective surgery	309 (31.7)	0 (0.0)		315 (31.3)	0 (0.0)		331 (29.1)	0 (0.0)	
Emergency surgery	656 (67.2)	3 (0.1)		679 (67.5)	0 (0.0)		794 (69.7)	0 (0.0)	
Admission diagnosis – no (%)*			< 0.001			< 0.001			< 0.001
Sepsis	411 (42.1)	1706 (72.7)		425 (42.2)	1802 (72.7)		493 (43.3)	2002 (72.4)	
Respiratory	63 (6.5)	304 (13.0)		66 (6.6)	312 (12.6)		91 (8.0)	357 (12.9)	
Gastrointestinal	115 (11.8)	57 (2.4)		120 (11.9)	61 (2.5)		135 (11.9)	71 (2.6)	
Cardiovascular	301 (30.8)	151 (6.4)		305 (30.3)	167 (6.7)		308 (27.0)	180 (6.5)	
Trauma	61 (6.2)	66 (2.8)		63 (6.3)	67 (2.7)		74 (6.5)	78 (2.8)	
Neurological	0 (0.0)	20 (0.9)		0 (0.0)	21 (0.8)		0 (0.0)	24 (0.9)	
Other	25 (2.6)	42 (1.8)		27 (2.7)	47 (1.9)		38 (3.3)	53 (1.9)	
ICU source of admission – no (%)*			< 0.001			< 0.001			< 0.001
Emergency room	2 (0.2)	1012 (43.1)		3 (0.3)	1067 (43.1)		3 (0.3)	1200 (43.4)	
Ward	3 (0.3)	1011 (43.1)		5 (0.5)	1075 (43.4)		8 (0.7)	1202 (43.5)	
Transferred from another hospital	40 (4.1)	323 (13.8)		44 (4.4)	335 (13.5)		48 (4.2)	363 (13.1)	
Operating room	931 (95.4)	0 (0.0)		954 (94.8)	0 (0.0)		1080 (94.8)	0 (0.0)	
PaO_2 / FiO_2 ratio, mmHg*	249.5 (176.0 – 340.0)	182.7 (125.0 – 260.0)	< 0.001	248.0 (175.1 – 340.0)	181.7 (124.0 – 260.0)	< 0.001	248.0 (175.1 – 340.0)	181.7 (124.0 – 260.0)	< 0.001
Sedatives and opioids – no (%)									
Opioids*[,a]	715 (73.3)	1789 (76.3)	0.070	717 (73.2)	1787 (76.3)	0.070	820 (74.7)	1999 (76.9)	0.151
Propofol*	898 (92.0)	1791 (76.3)	< 0.001	899 (91.8)	1790 (76.4)	< 0.001	1006 (91.6)	1985 (76.3)	< 0.001

Midazolam*	145 (14.9)	900 (38.4)	< 0.001	148 (15.1)	897 (38.3)	< 0.001	167 (15.2)	995 (38.3)	< 0.001
Ketamine*	36 (3.7)	180 (7.7)	< 0.001	36 (3.7)	180 (7.7)	< 0.001	38 (3.5)	197 (7.6)	< 0.001
Dexmedetomidine*	5 (0.5)	59 (2.5)	< 0.001	5 (0.5)	59 (2.5)	< 0.001	5 (0.5)	73 (2.8)	< 0.001
Clinical outcomes									
90-day mortality – no (%)	240 (24.6)	731 (31.2)	< 0.001	248 (24.7)	780 (31.5)	< 0.001	268 (23.5)	867 (31.4)	< 0.001
Coma and delirium free days	24.0 (15.0 – 26.0)	23.0 (9.0 – 26.0)	< 0.001	24.0 (15.0 – 26.0)	23.0 (8.0 – 26.0)	< 0.001	24.0 (16.0 – 26.0)	23.0 (9.0 – 26.0)	< 0.001
Ventilator-free days	24.0 (6.0 – 26.0)	22.0 (0.0 – 25.0)	< 0.001	24.0 (6.2 – 26.0)	21.0 (0.0 – 25.0)	< 0.001	24.0 (10.0 – 26.0)	21.0 (0.0 – 25.0)	< 0.001

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding.

APACHE: Acute Physiology and Chronic Health Evaluation; ICU: intensive care unit

* Variables considered in the cluster process

[a] Opioids aggregate the use of morphine and/or fentanyl

2.3. E-TABLE 3: ADVERSE AND SERIOUS ADVERSE EVENTS BY GROUP ALLOCATION – AGE AND CLUSTERS

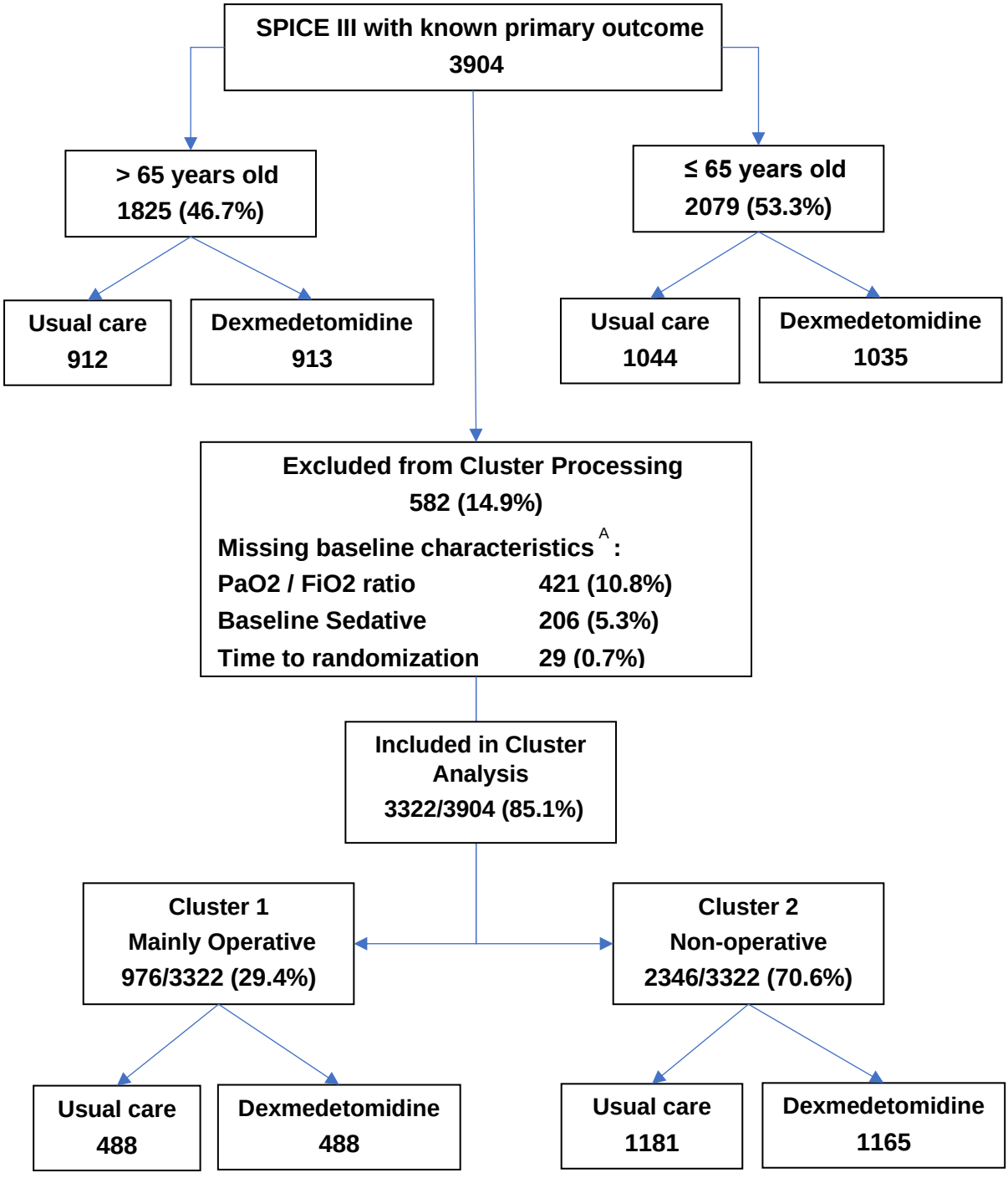
	≤ 65 Years		> 65 Years		Cluster 1		Cluster 2	
	Dexmedetomidine (*n* = 1035)	Usual Care (*n* = 1044)	Dexmedetomidine (*n* = 913)	Usual Care (*n* = 912)	Dexmedetomidine (*n* = 488)	Usual Care (*n* = 488)	Dexmedetomidine (*n* = 1165)	Usual Care (*n* = 1181)
One or more AE	98 (9.5)	17 (1.6)	90 (9.9)	18 (2.0)	45 (9.2)	7 (1.4)	117 (10.0)	23 (1.9)
One or more SAE	28 (2.7)	3 (0.3)	23 (2.5)	4 (0.4)	8 (1.6)	1 (0.2)	32 (2.7)	6 (0.5)
Adverse events								
Bradycardia	52 (5.0)	6 (0.6)	52 (5.7)	4 (0.4)	22 (4.5)	0 (0.0)	66 (5.7)	6 (0.5)
Hypotension	29 (2.8)	5 (0.5)	33 (3.6)	6 (0.7)	17 (3.5)	3 (0.6)	37 (3.2)	8 (0.7)
Other	31 (3.0)	9 (0.9)	23 (2.5)	12 (1.3)	15 (3.1)	5 (1.0)	34 (2.9)	15 (1.3)
SAEs								
Bradycardia	7 (0.7)	0 (0.0)	7 (0.8)	1 (0.1)	2 (0.4)	0 (0.0)	8 (0.7)	1 (0.1)
Hypotension	5 (0.5)	0 (0.0)	4 (0.4)	1 (0.1)	3 (0.6)	0 (0.0)	5 (0.4)	1 (0.1)
Asystole	8 (0.8)	1 (0.1)	6 (0.7)	1 (0.1)	2 (0.4)	0 (0.0)	10 (0.9)	2 (0.2)
Other	10 (1.0)	2 (0.2)	6 (0.7)	1 (0.1)	2 (0.4)	1 (0.2)	10 (0.9)	2 (0.2)
Uncontrolled agitation	35 (3.4)	48 (4.6)	6 (0.7)	29 (3.2)	6 (1.2)	18 (3.7)	29 (2.5)	45 (3.8)

Abbreviations: adverse events; SAE: serious adverse events

Table describes number (%) who experienced each event on one or more occasions. Patients can have multiple AEs/SAEs. AEs and SAEs were defined in the protocol, however, events were reported by site investigators and were not systematically collected in both groups. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients

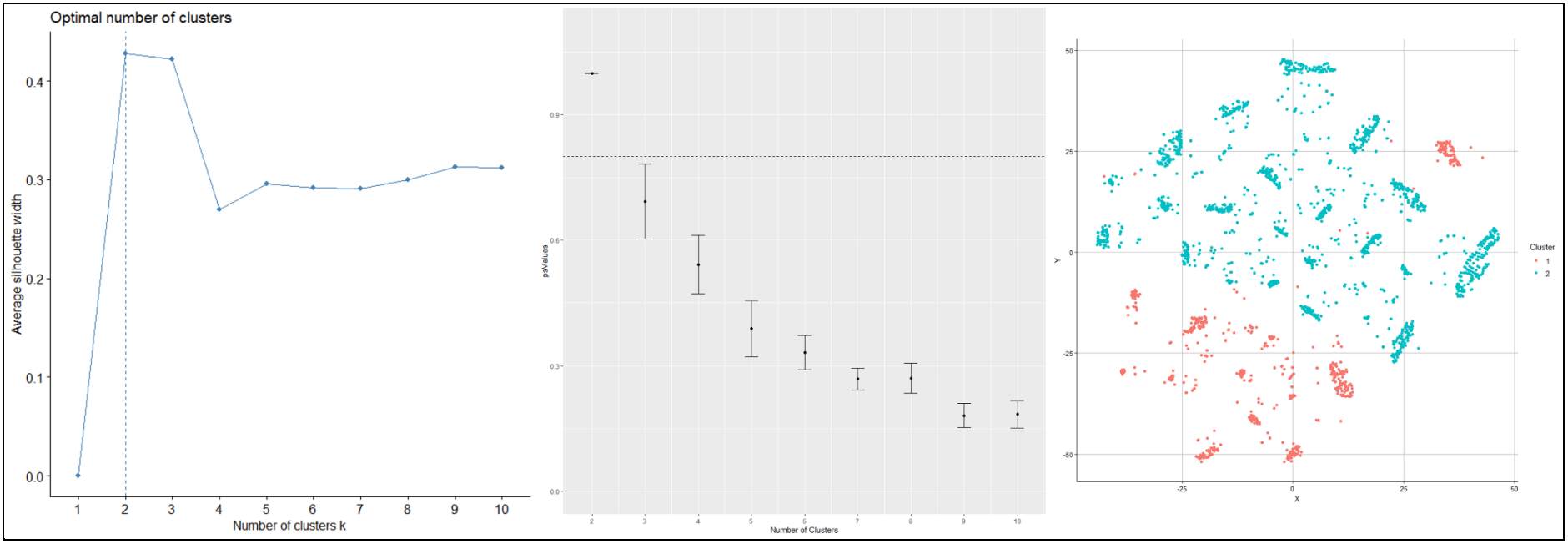
3. E- FIGURES

3.1. E-FIGURE 1: STUDY FLOW DIAGRAM



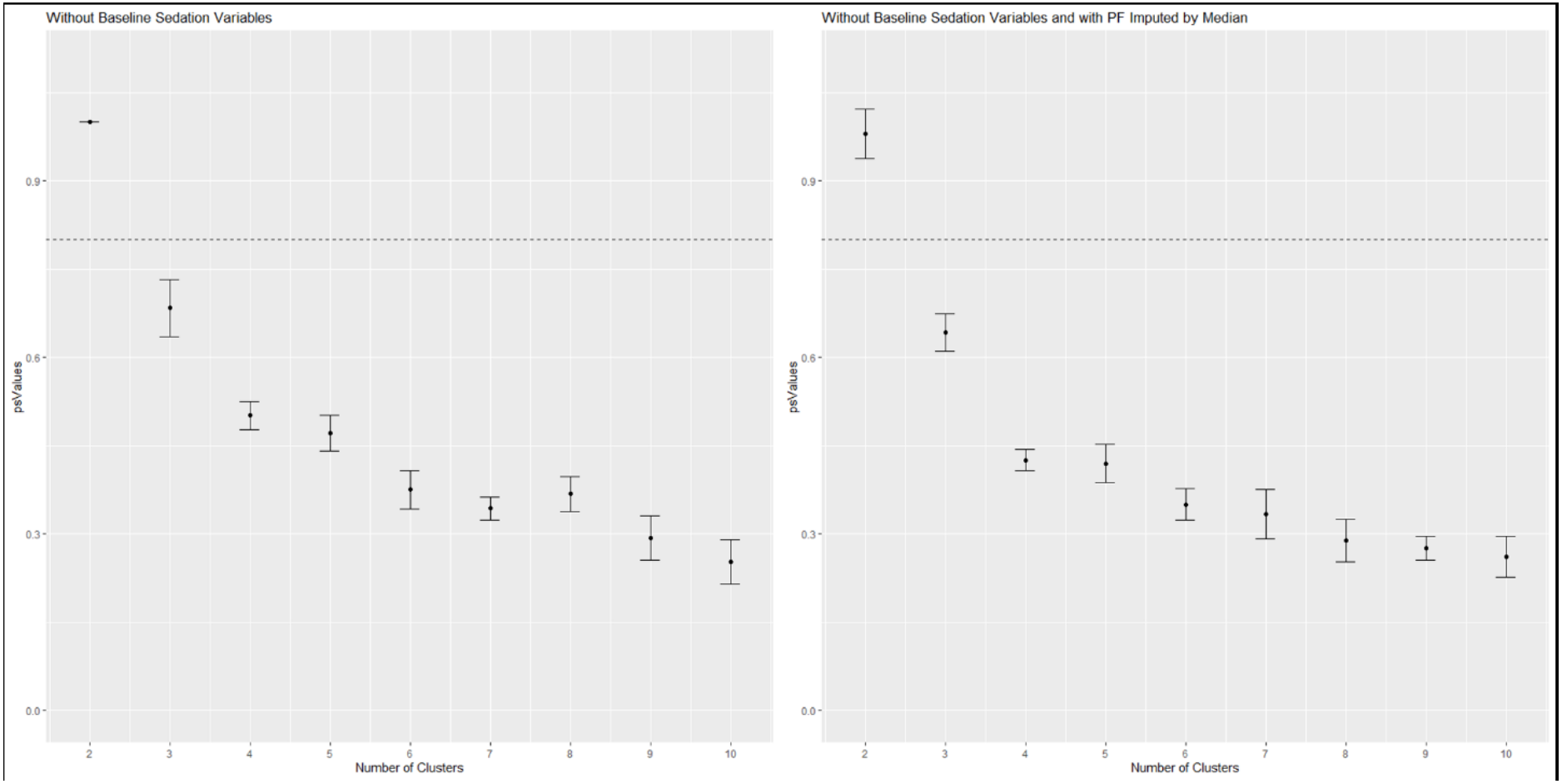
A Patients may have more than one missing data

3.2. E-FIGURE 2A - OPTIMAL NUMBER OF CLUSTERS IDENTIFIED IN THE DATASET

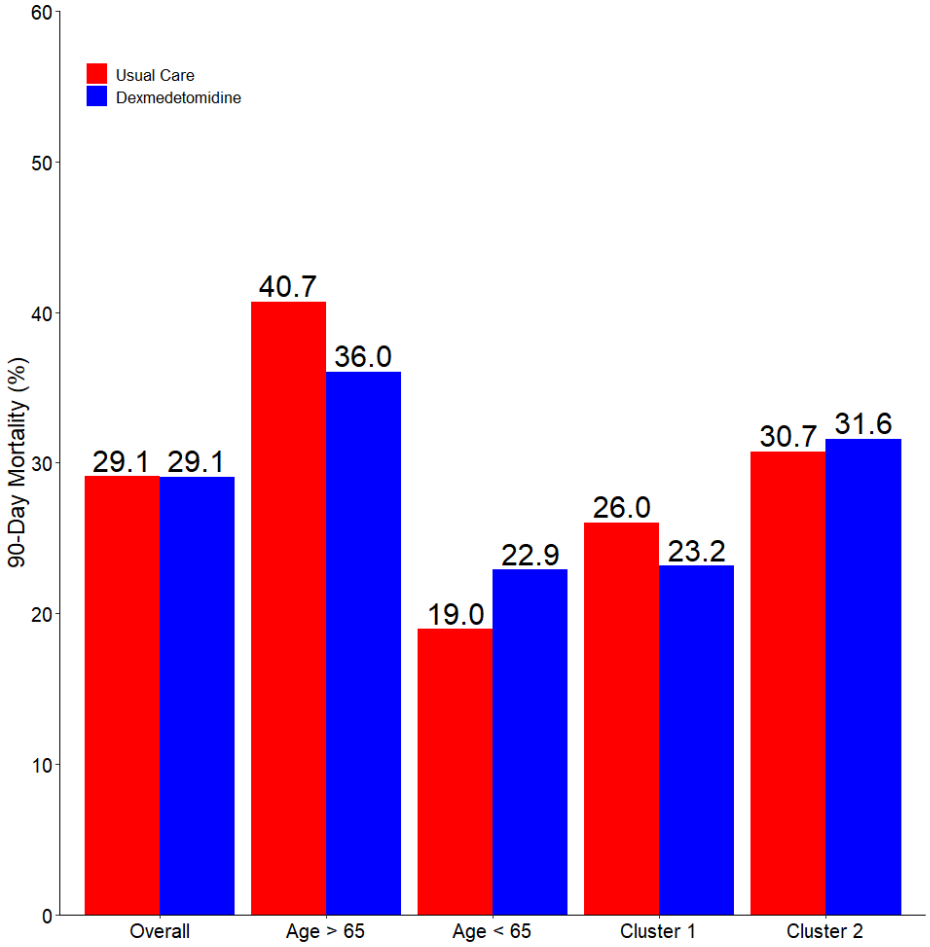


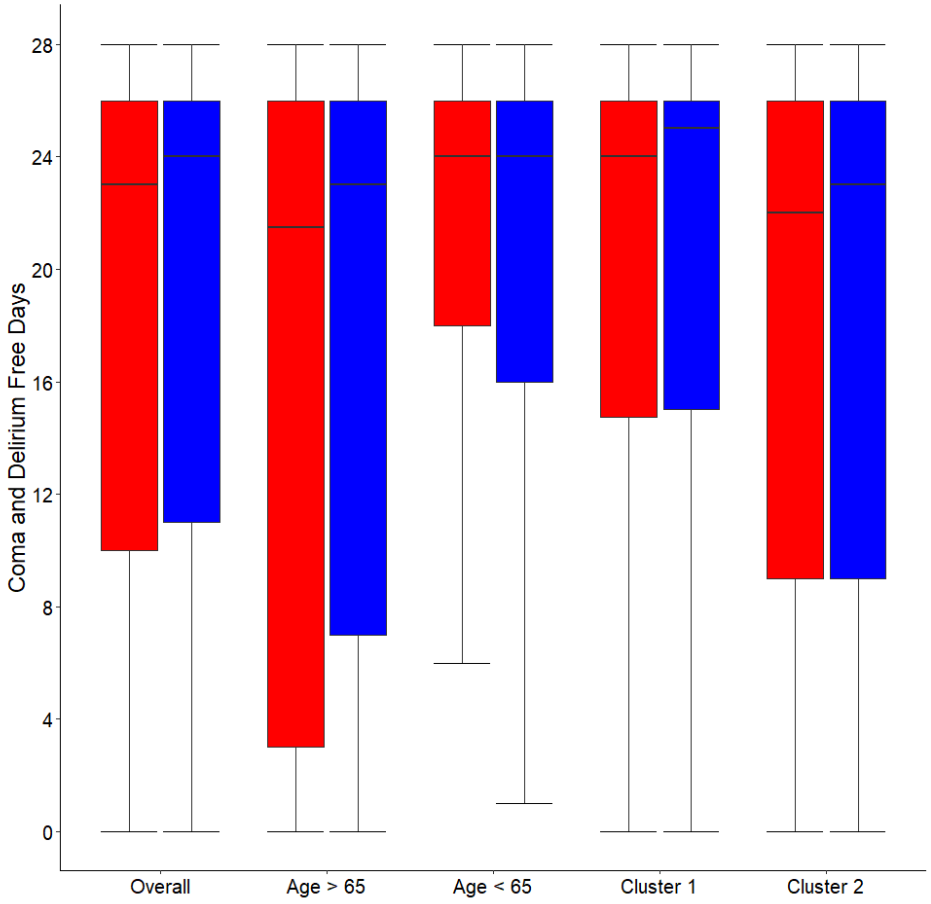
Left panel: This method computes partitioning around medoids (PAM) algorithm using different values of clusters k. Next, the average clusters silhouette is drawn according to the number of clusters. The average silhouette measures the quality of a clustering. A high average silhouette width indicates a good clustering. The optimal number of clusters k is the one that maximize the average silhouette over a range of possible values for k.
Middle panel: Prediction strength according to *kamila* algorithm for different number of simulated clusters after cross–validation. Two clusters provided the highest prediction strength values (psValues) and this value is higher than the prediction strength threshold.
Right panel: tSNE plot using Gower's distance with colors based on clusters found by *kamila* algorithm. Although some overlap between clusters based on Gower's distance is seen, there is a considerable difference between the two clusters found by *kamila*.
kamila is an iterative clustering method that equitably balances the contribution of continuous and categorical variables. Gower Distance is a distance measure that can be used to calculate the distance between two entities whose attributes have a mix of categorical and numerical value

3.2.1. E-FIGURE 2B – SENSITIVITY ANALYSIS FOR THE CLUSTERING PROCESS



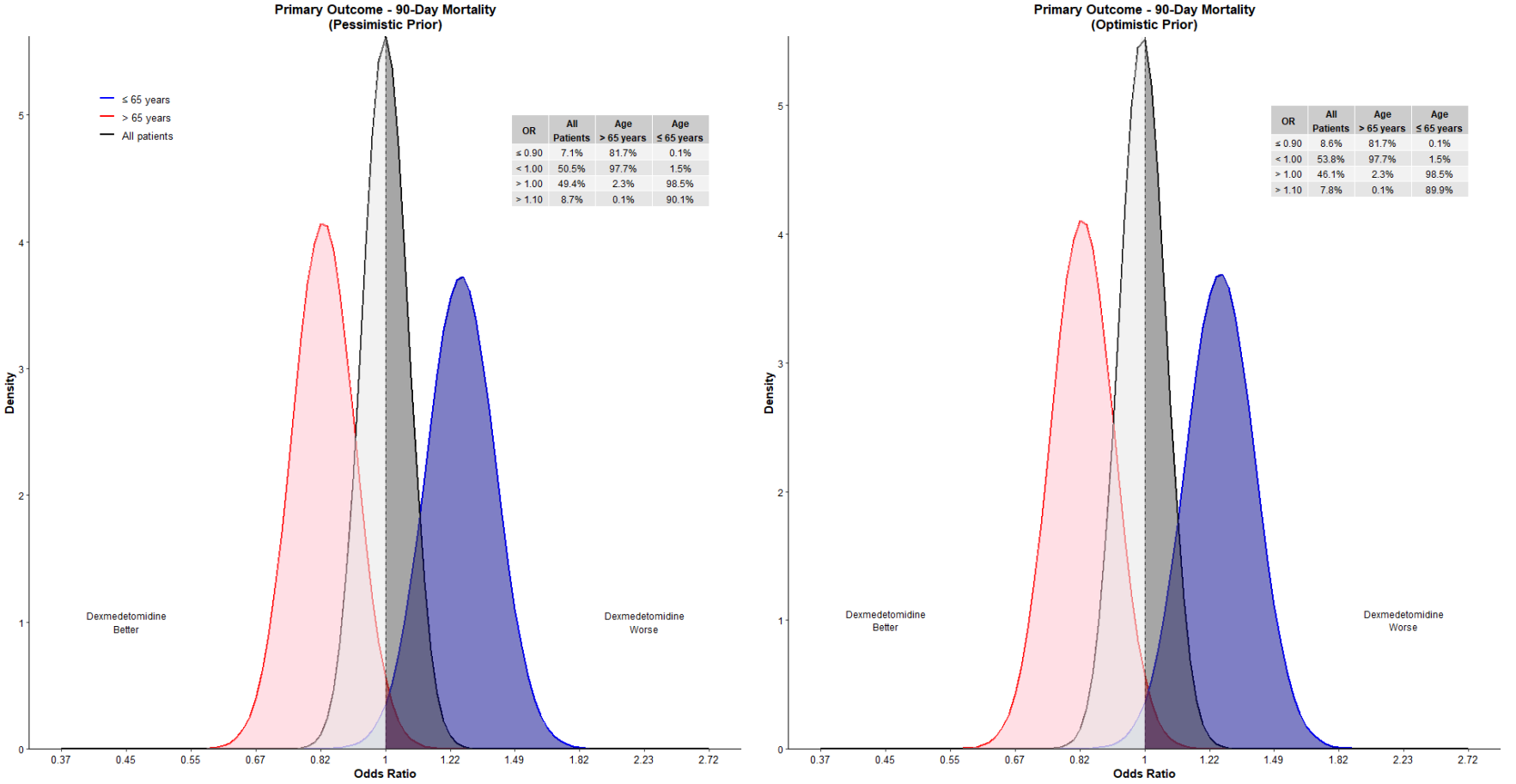
3.3. E-FIGURE 3- 90-DAY MORTALITY RATE AND COMA AND DELIRIUM FREE DAYS ACCORDING TO SUBGROUPS





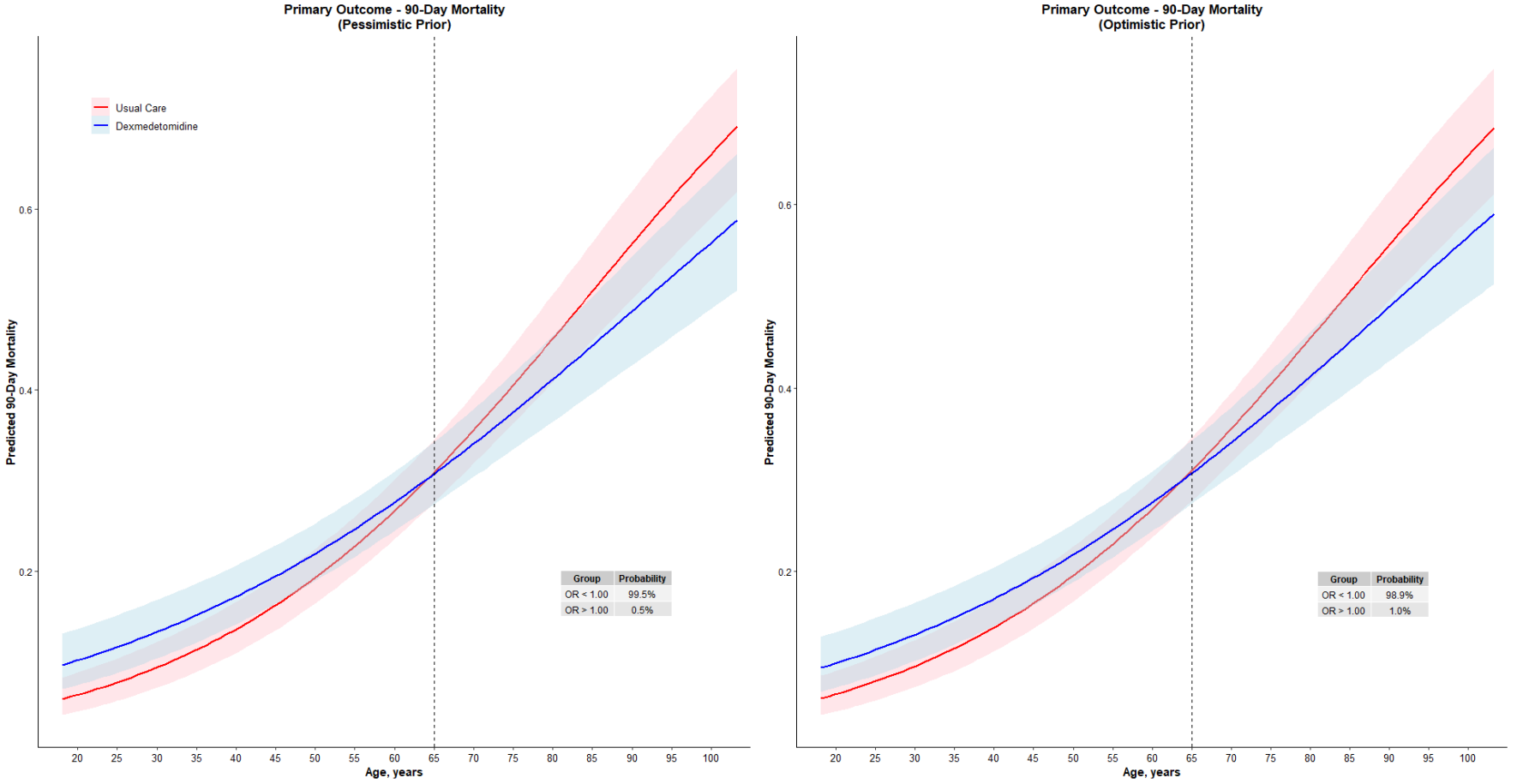
Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients

3.4. E-FIGURE 4 - HETEROGENEITY OF TREATMENT EFFECT FOR 90-DAY MORTALITY ACCORDING TO CATEGORIES OF AGE AND WITH DIFFERENT PRIORS



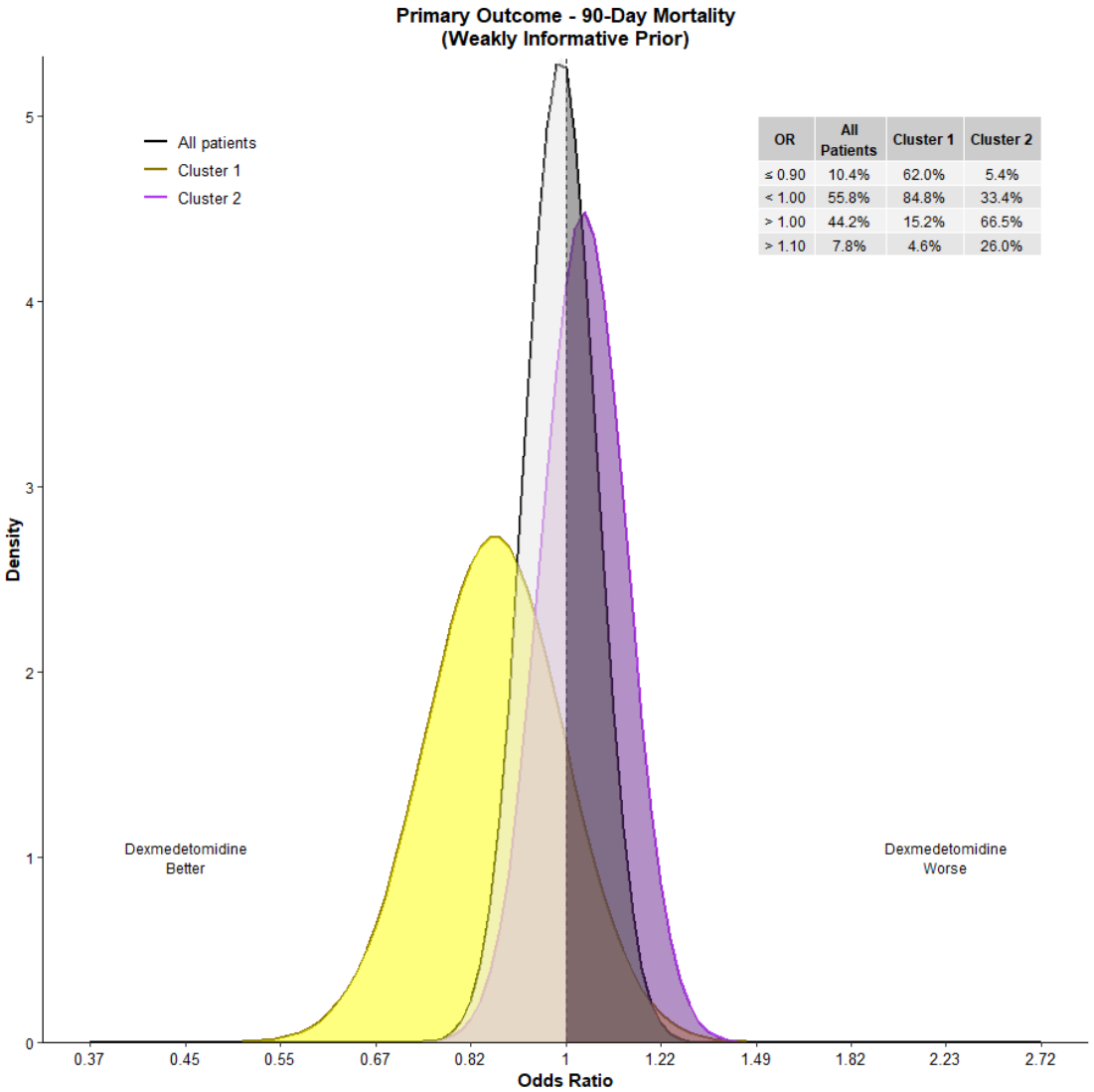
Data is the posterior distribution of odds ratio in subgroups and overall cohort. Light red, gray and blue area represent areas where dexmedetomidine is beneficial, while dark red, gray and blue are represent areas where dexmedetomidine is harmful.
OR: odds ratio

3.5. E-FIGURE 5 - MARGINAL EFFECT PLOT FOR THE INTERACTION BETWEEN THE ALLOCATION GROUP AND AGE WITH DIFFERENT PRIORS FOR 90-DAY MORTALITY



OR is the effect estimate for the interaction among allocation group and age. OR < 1.00 represent a favorable outcome with the use of dexmedetomidine with increased age.
OR: odds ratio

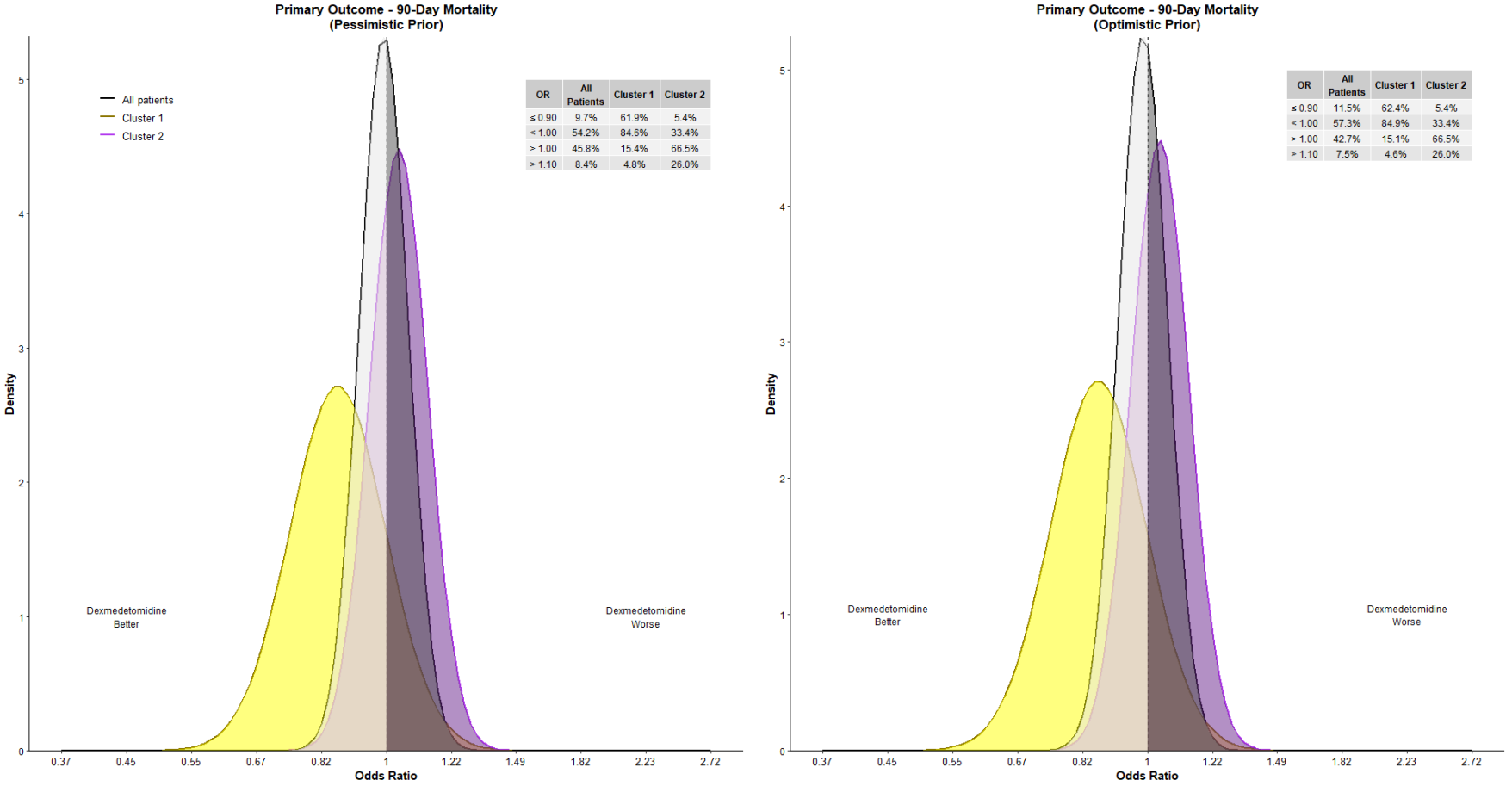
3.6. E FIGURE 6 - CLUSTER RELATED HETEROGENEITY OF TREATMENT EFFECT – DEXMEDETOMIDINE AND MORTALITY



OR	All Patients	Cluster 1	Cluster 2
≤ 0.90	10.4%	62.0%	5.4%
< 1.00	55.8%	84.8%	33.4%
> 1.00	44.2%	15.2%	66.5%
> 1.10	7.8%	4.6%	26.0%

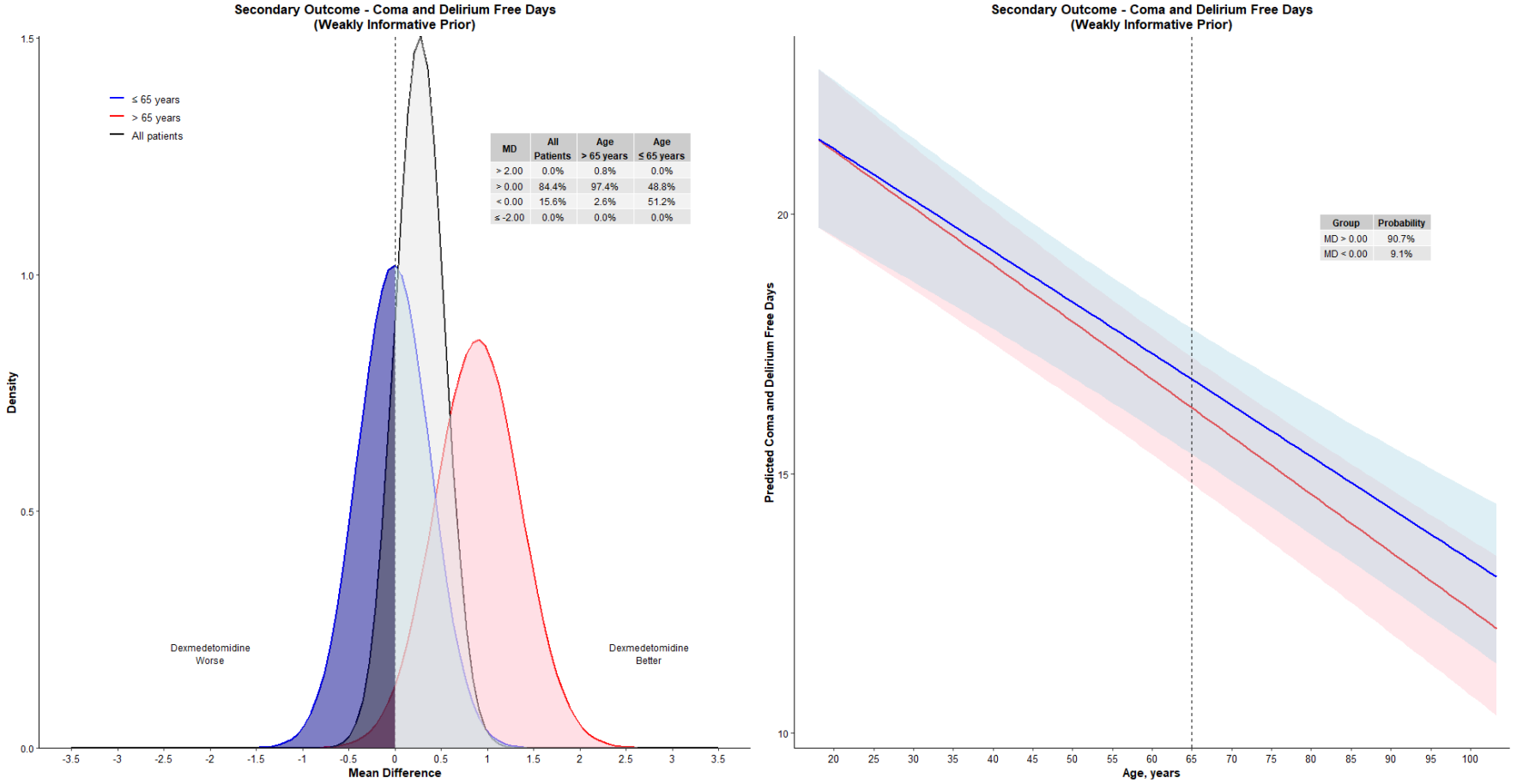
The posterior distribution of mortality, depicted as odds ratios. OR < 1.00 represent a favorable outcome with the use of dexmedetomidine. The probability of benefit is 84.8% in patients in cluster 1 with 66.5% probability of harm in patients in cluster 2. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients.

3.7. E-FIGURE 7 - HETEROGENEITY OF TREATMENT EFFECT FOR 90-DAY MORTALITY ACCORDING TO THE CLUSTERS AND WITH DIFFERENT PRIORS



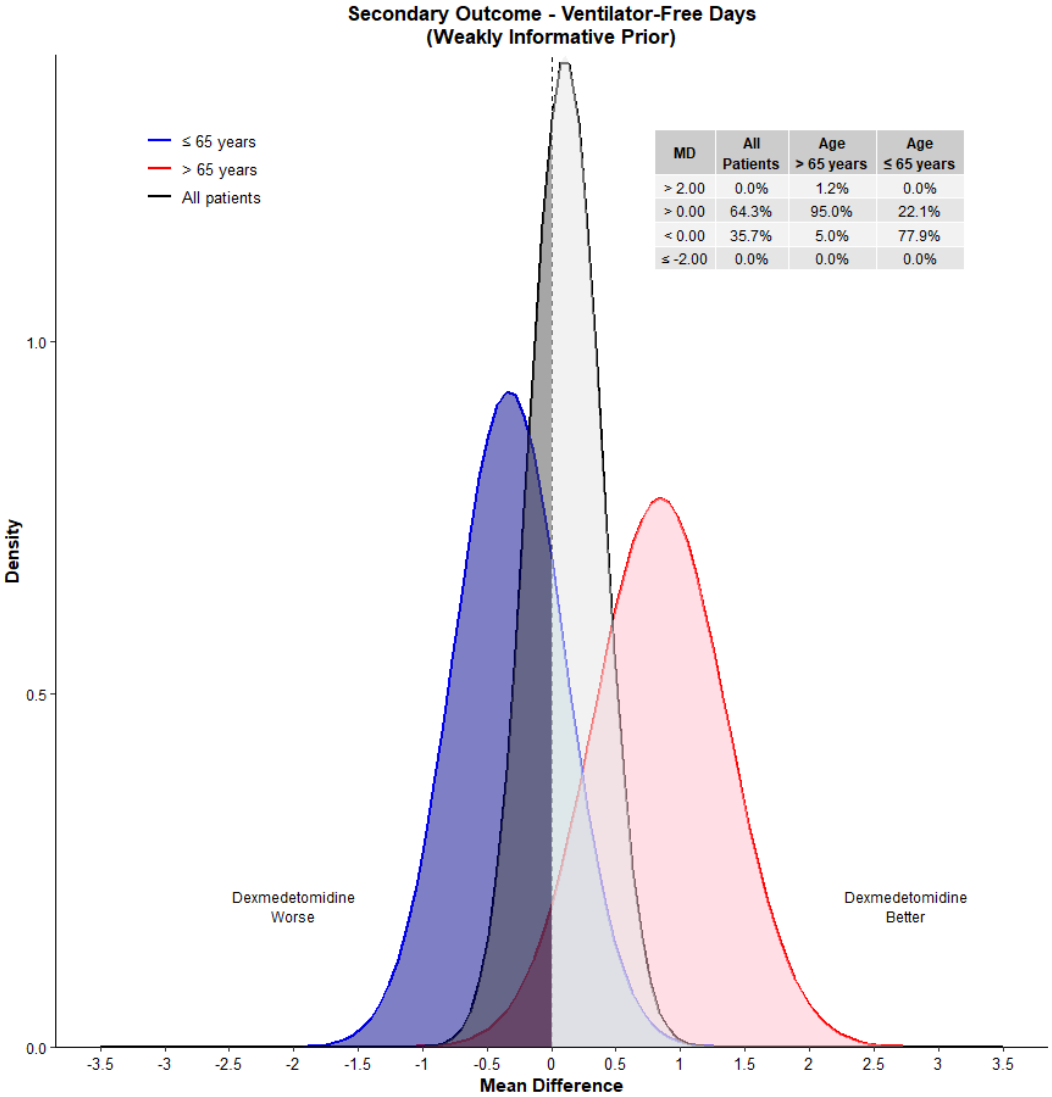
Data is the posterior distribution of odds ratio in subgroups and overall cohort. OR < 1.00 represent a favorable outcome with the use of dexmedetomidine. Light yellow, gray and purple area represent areas where dexmedetomidine is beneficial, while dark yellow, gray and purple areas represent areas where dexmedetomidine is harmful. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients.

3.8. E FIGURE 8 - HETEROGENEITY OF TREATMENT EFFECT OF COMA AND DELIRIUM FREE DAYS ACCORDING TO CATEGORIES OF AGE AND MARGINAL EFFECT PLOT FOR THE INTERACTION BETWEEN THE ALLOCATION GROUP AND AGE FOR COMA AND DELIRIUM FREE DAYS



Data is the posterior distribution of mean difference in subgroups and overall cohort. Priors were weakly informative. Light red, gray and blue area represent areas where dexmedetomidine is beneficial, while dark red, gray and blue areas represent areas where dexmedetomidine is harmful. MD is the effect estimate for the interaction among allocation group and age. MD > 0.00 represents a favorable outcome with the use of dexmedetomidine and with increased age. Priors were weakly informative (described in **eMethods** in **Online Supplement**).
The potential scale reduction factor (Rhat) was < 1.01 for all parameters in both models (biggest Rhat was 1.000146 for the primary outcome and 1.000225 for the secondary outcome).
MD: mean difference

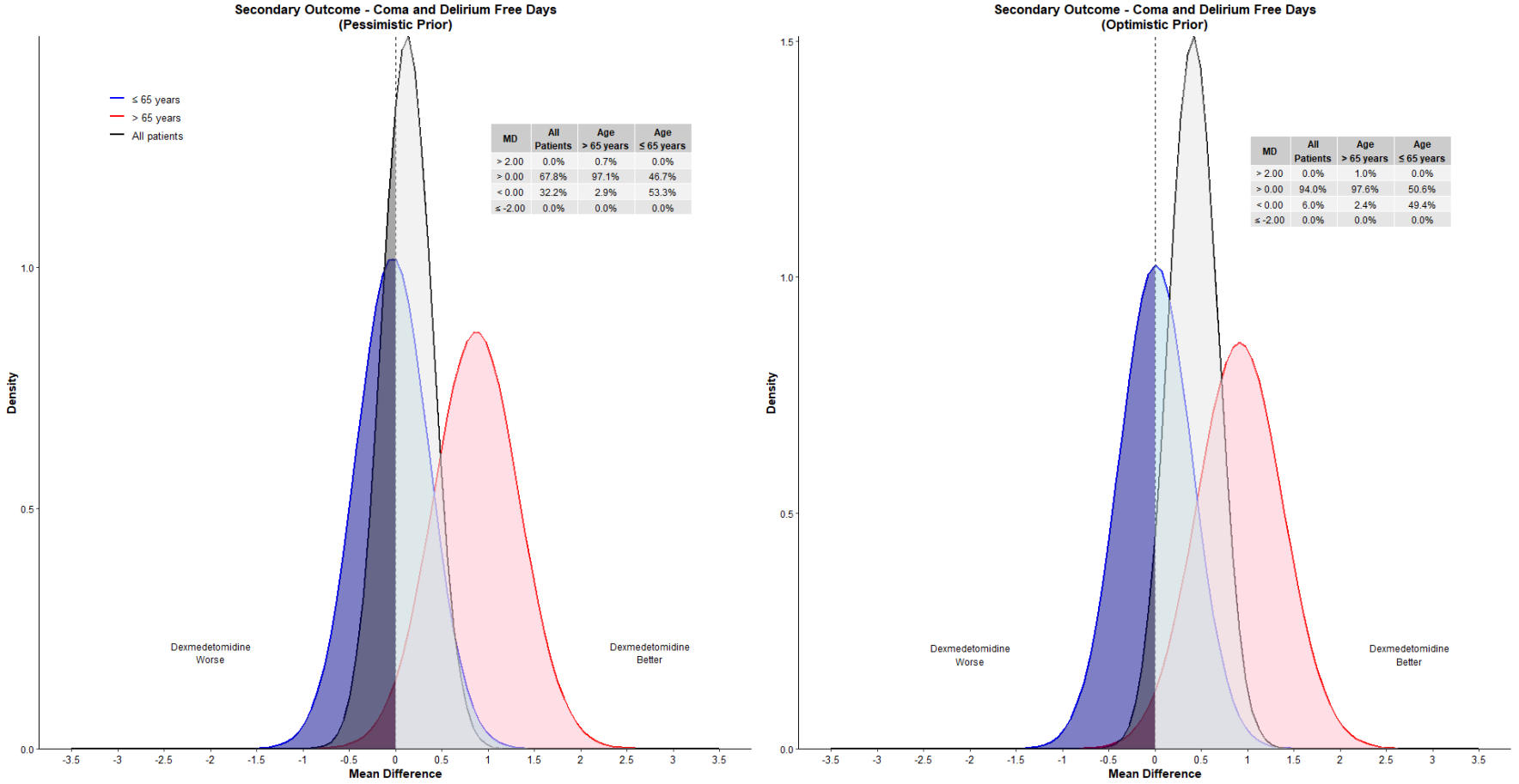
3.9. E-FIGURE 9 - HETEROGENEITY OF TREATMENT EFFECT OF VENTILATOR-FREE DAYS TO CATEGORIES OF AGE



Data is the posterior distribution of mean difference in subgroups and overall cohort. Priors were weakly informative. Light red, gray and blue area represent areas where dexmedetomidine is beneficial, while dark red, gray and blue areas represent areas where dexmedetomidine is harmful.

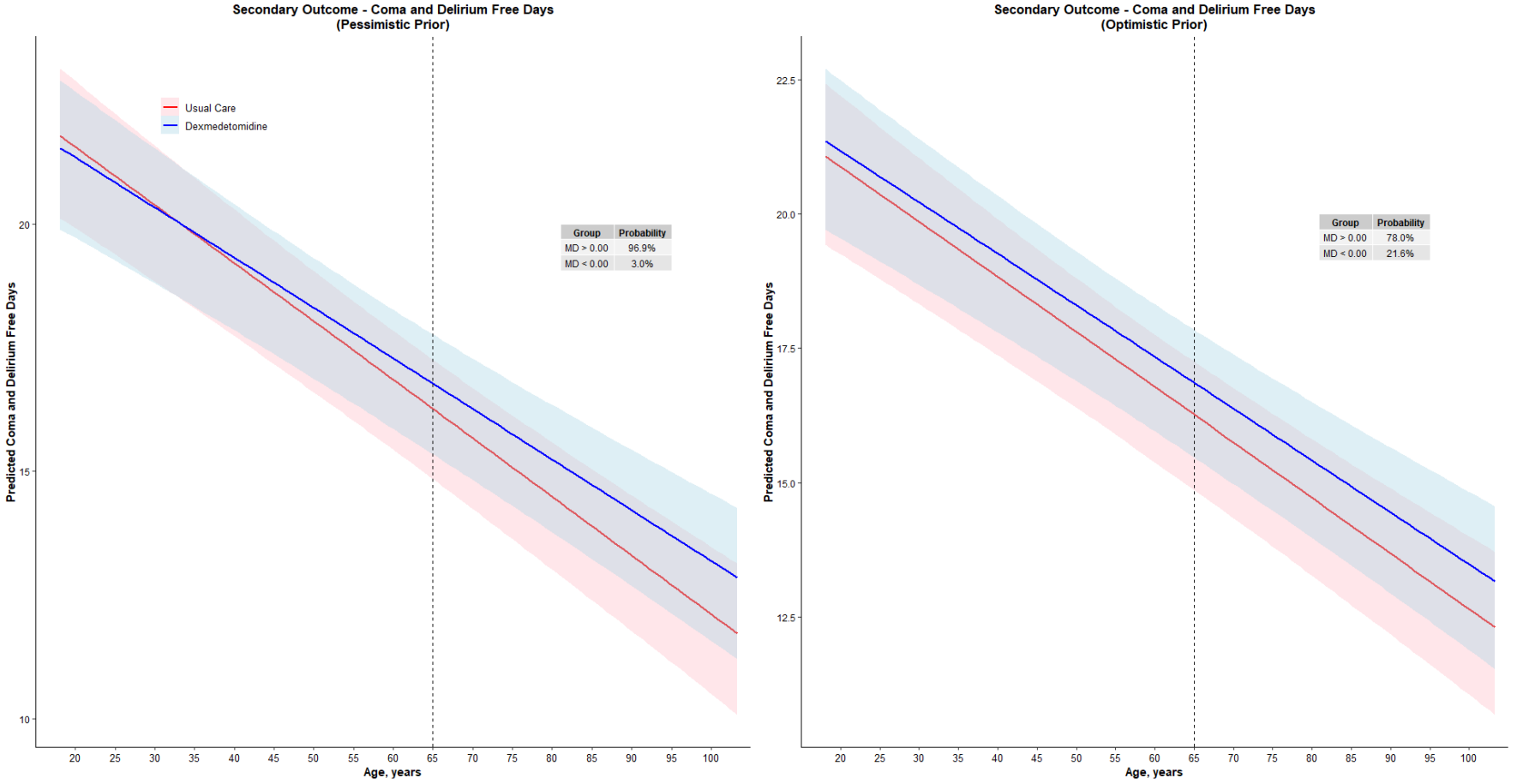
MD: mean difference

3.10. E-FIGURE 10 - HETEROGENEITY OF TREATMENT EFFECT OF COMA AND DELIRIUM FREE DAYS ACCORDING TO CATEGORIES OF AGE AND WITH DIFFERENT PRIORS



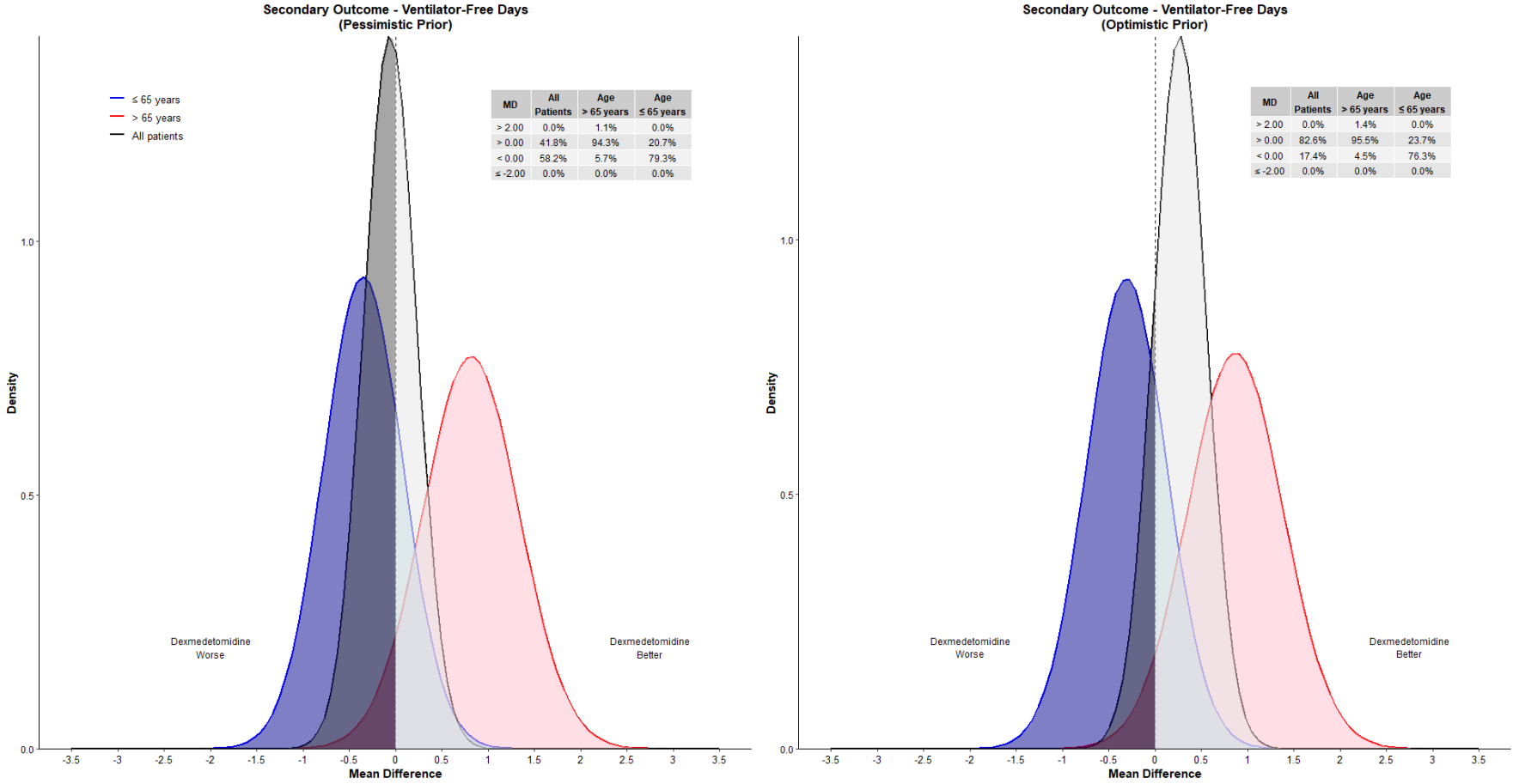
Data is the posterior distribution of mean difference in subgroups and overall cohort. Light red, gray and blue area represent areas where dexmedetomidine is beneficial, while dark red, gray and blue are represent areas where dexmedetomidine is harmful.
MD: mean difference

3.11. E-FIGURE 11 - MARGINAL EFFECT PLOT FOR THE INTERACTION BETWEEN THE ALLOCATION GROUP AND AGE WITH DIFFERENT PRIORS FOR COMA AND DELIRIUM FREE DAYS



MD is the effect estimate for the interaction among allocation group and age. MD > 0.00 represent a favorable outcome with the use of dexmedetomidine with increased age.
MD: mean difference

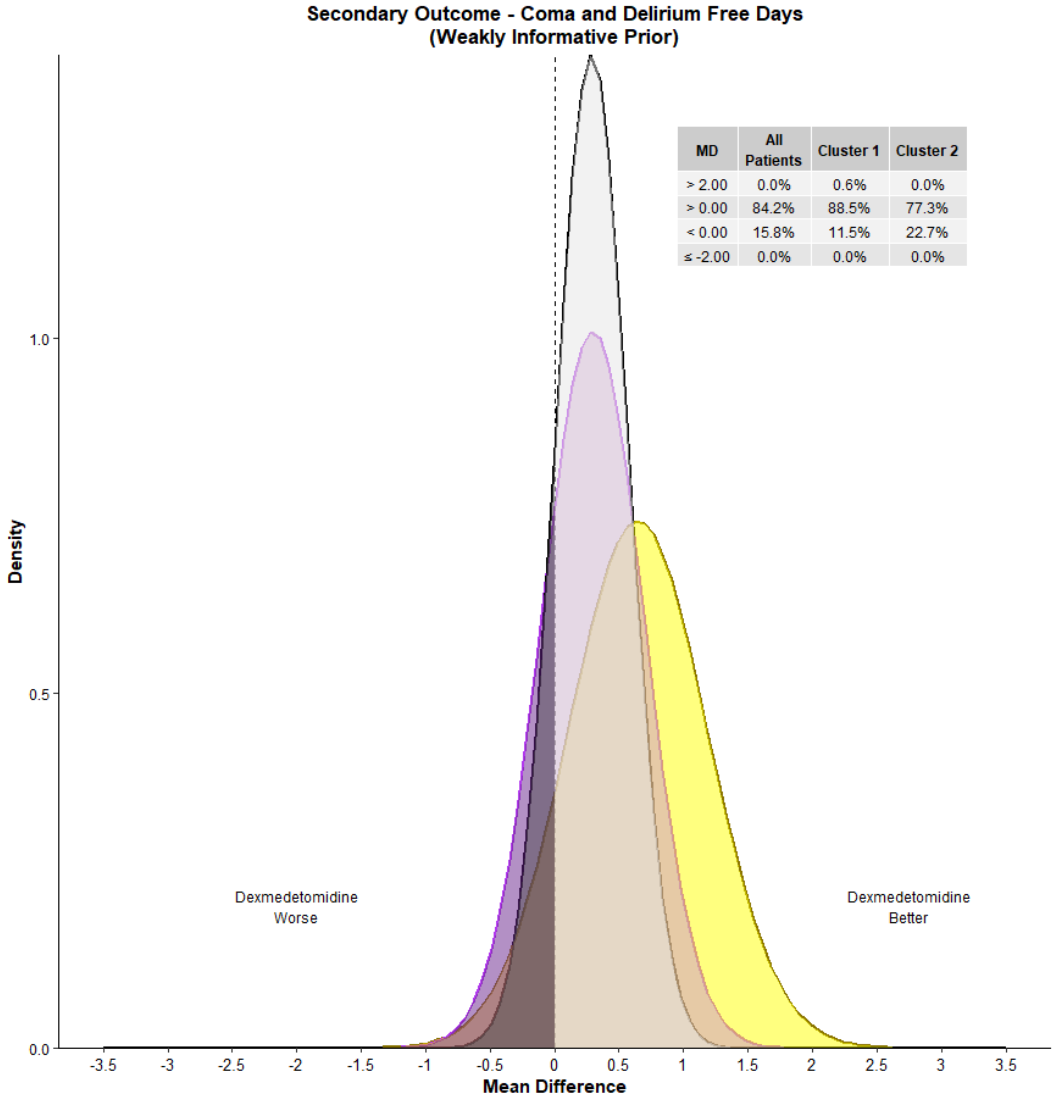
3.12. E-FIGURE 12 - HETEROGENEITY OF TREATMENT EFFECT OF VENTILATOR-FREE DAYS ACCORDING TO CATEGORIES OF AGE AND WITH DIFFERENT PRIORS



Data is the posterior distribution of mean difference in subgroups and overall cohort. Light red, gray and blue area represent areas where dexmedetomidine is beneficial, while dark red, gray and blue are represent areas where dexmedetomidine is harmful.

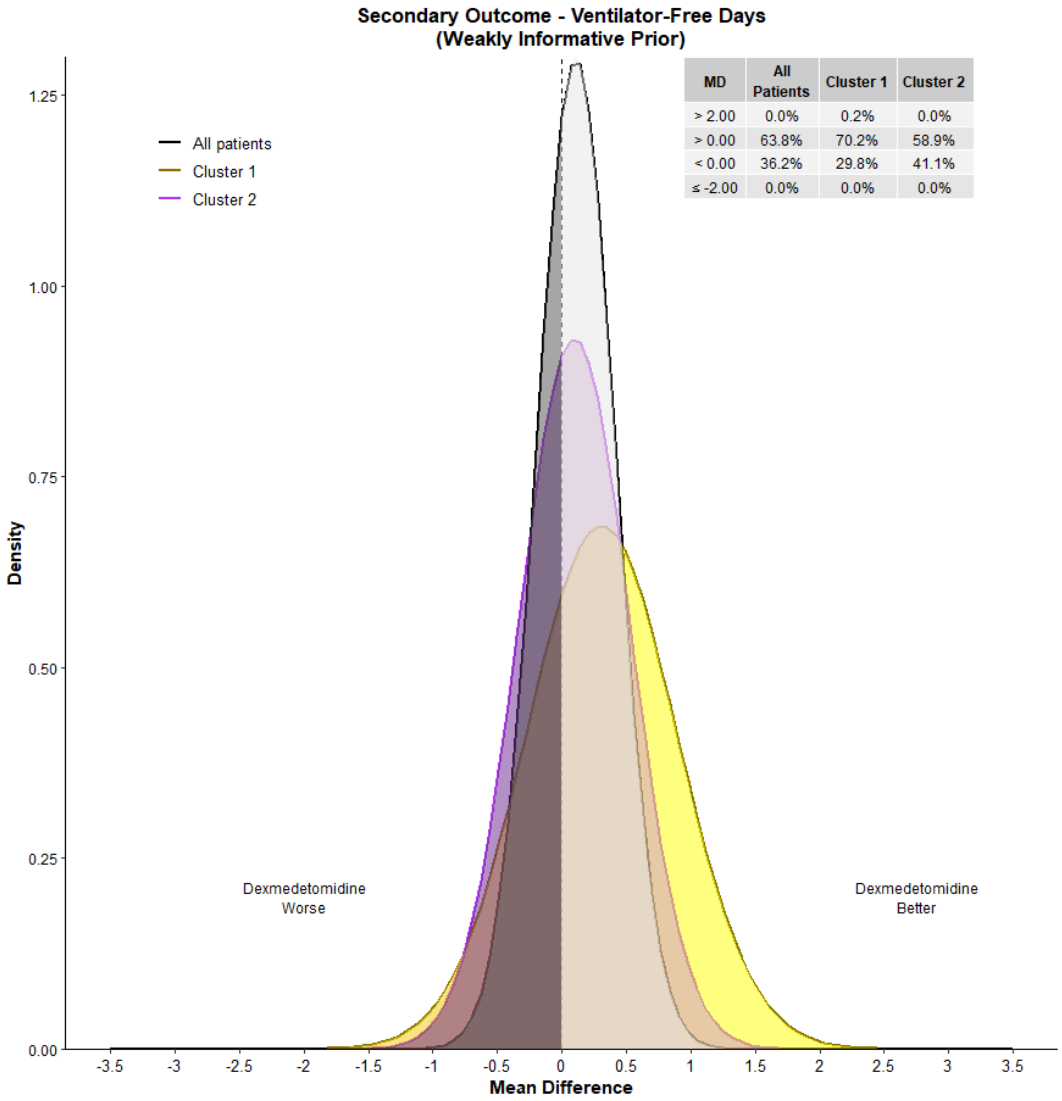
MD: mean difference

3.13. E-FIGURE 13 - HETEROGENEITY OF TREATMENT EFFECT OF COMA AND DELIRIUM FREE DAYS ACCORDING TO THE CLUSTERS



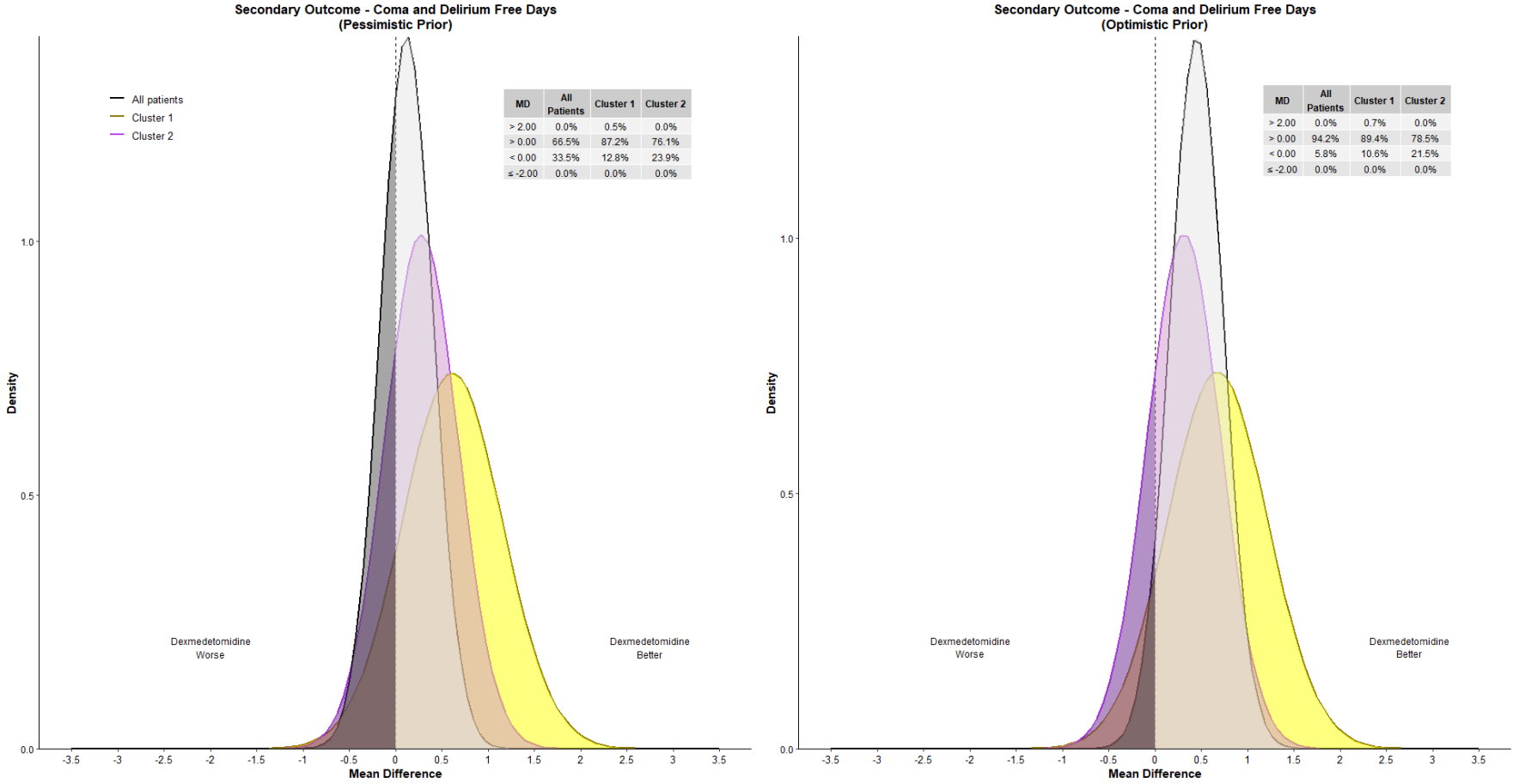
Data represent the posterior distribution of mean difference in subgroups and overall cohort. Light yellow, gray and purple areas represent areas where dexmedetomidine is beneficial, while dark yellow, gray and purple areas represent areas where dexmedetomidine is harmful.
MD: mean difference

3.14. E-FIGURE 14 - HETEROGENEITY OF TREATMENT EFFECT OF VENTILATOR-FREE DAYS ACCORDING TO THE CLUSTERS



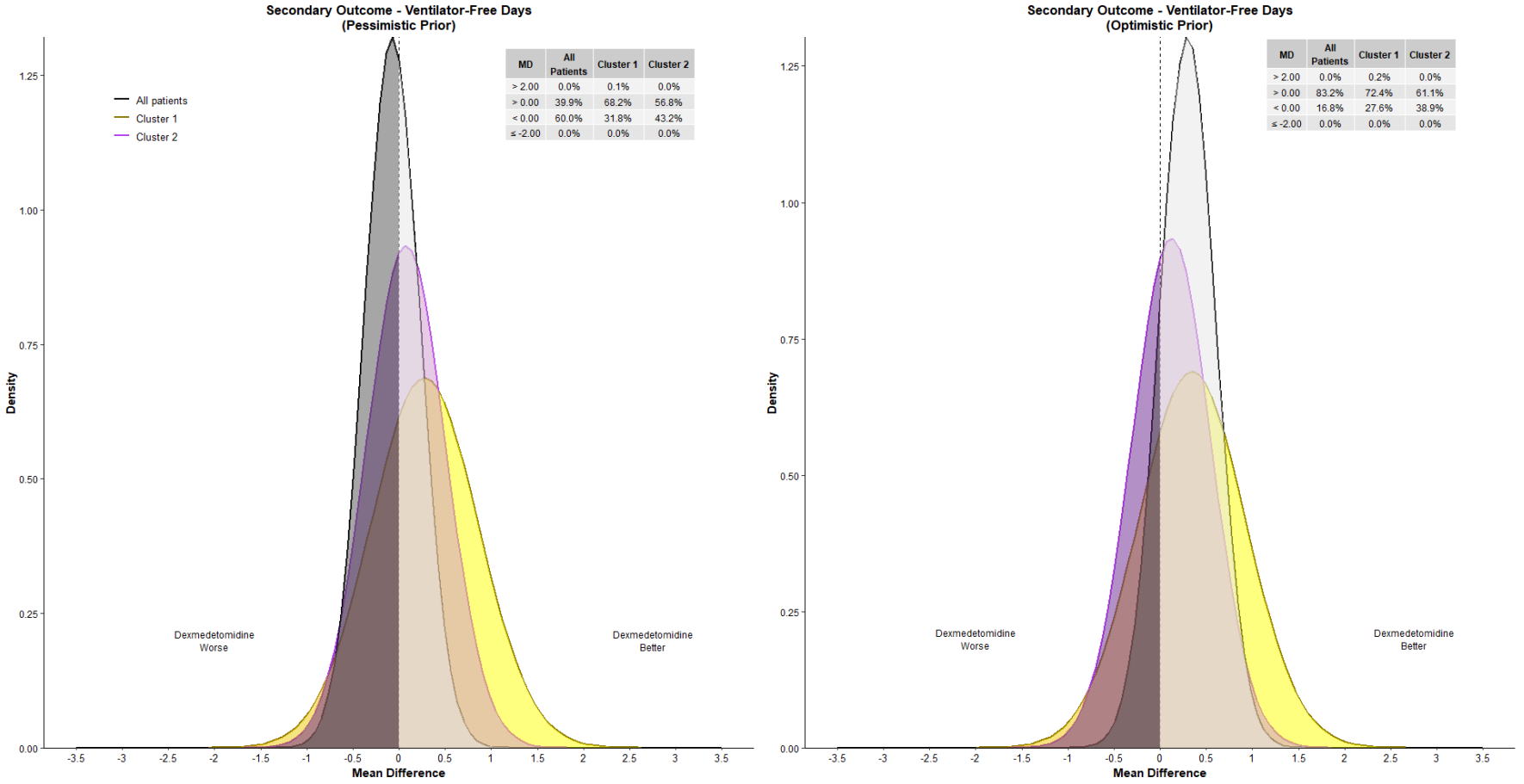
Data is the posterior distribution of mean difference in subgroups and overall cohort. Light yellow, gray and purple area represent areas where dexmedetomidine is beneficial, while dark yellow, gray and purple areas represent areas where dexmedetomidine. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients.
MD: mean difference

3.15. E-FIGURE 15 - HETEROGENEITY OF TREATMENT EFFECT FOR COMA AND DELIRIUM FREE DAYS ACCORDING TO THE CLUSTERS AND WITH DIFFERENT PRIORS



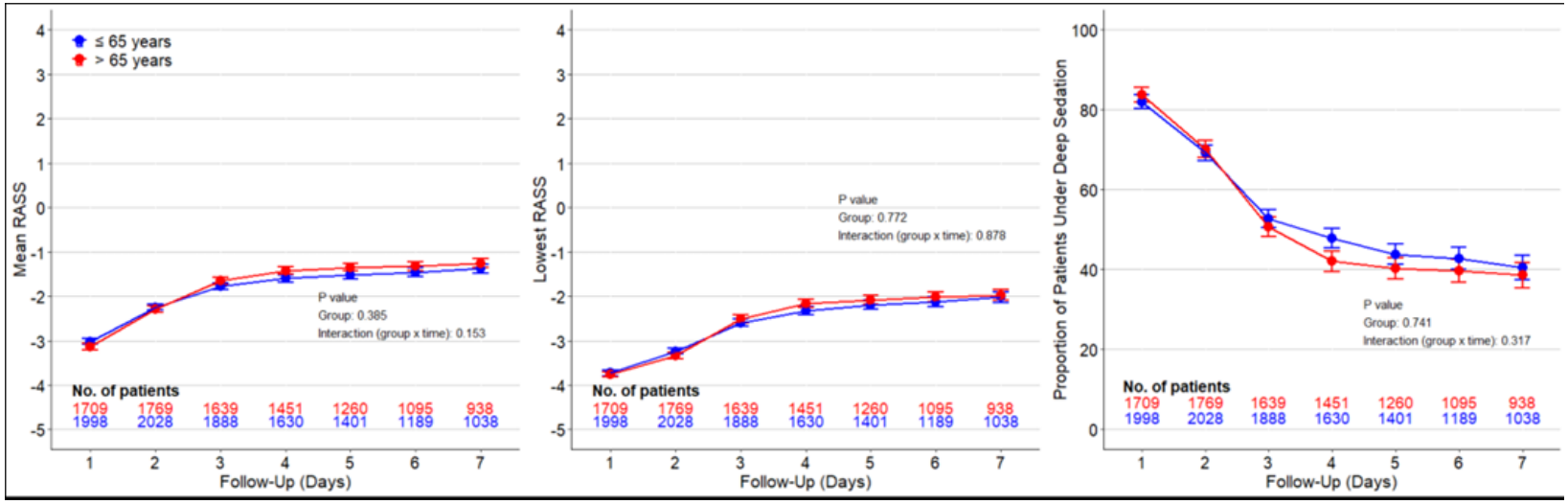
Data is the posterior distribution of mean difference in subgroups and overall cohort. Light yellow, gray and purple area represent areas where dexmedetomidine is beneficial, while dark yellow, gray and purple areas represent areas where dexmedetomidine is harmful. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients.
MD: mean difference

3.16. E-FIGURE 16 - HETEROGENEITY OF TREATMENT EFFECT FOR VENTILATOR-FREE DAYS ACCORDING TO THE CLUSTERS AND WITH DIFFERENT PRIORS

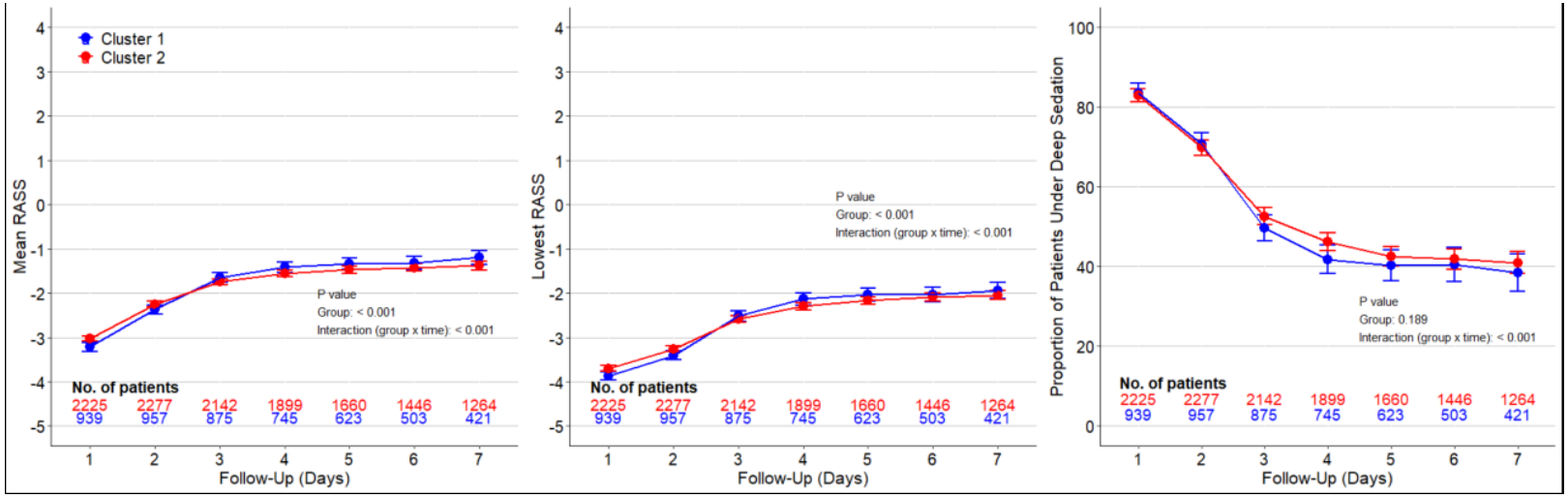


Data is the posterior distribution of mean difference in subgroups and overall cohort. Light yellow, gray and purple area represent areas where dexmedetomidine is beneficial, while dark yellow, gray and purple areas represent areas where dexmedetomidine is harmful. Cluster 1 is predominantly operative patients and cluster 2 is non-operative patients.
MD: mean difference

3.17. E-FIGURE 17-A – SEDATION LEVEL IN THE FIRST 7 DAYS IN YOUNG VS OLDER PATIENTS



3.18. E-FIGURE 17-B – SEDATION LEVEL IN THE FIRST 7 DAYS IN CLUSTER 1 VS CLUSTER 2



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5. SPICE III STUDY INVESTIGATORS:

Site investigators (alphabetically by institution and all in Australia unless specified as New Zealand [NZ], Ireland [IR], Italy [IT], Malaysia [MY], Saudi Arabia [SA], Switzerland [CH] or United Kingdom [UK]):

Albury Base Hospital, Albury, NSW, C. Mashonganyika, H. McKee, A. Tonks; Altnagelvin Area Hospital, Londonderry, UK, A. Donnelly, N. Hemmings, S. O'Kane; Auckland City Hospital CVICU, Auckland, NZ, A. Blakemore, M. Butler, K. Cowdrey, J. Dalton, E. Gilder, S. Long, L. McCarthy, S. McGuinness, R. Parke; Auckland City Hospital DCCM, Auckland, NZ, Y. Chen, C. McArthur, R. McConnochie, L. Newby; Austin Health, Melbourne, VIC, R. Bellomo, G. Eastwood, L. Peck, H. Young; Bendigo Hospital, Bendigo, VIC, C. Boschert, J. Edington, J. Fletcher, J. Smith; Blacktown Hospital, Sydney, NSW, K. Nand, A. Raza, T. Sara; Bristol Royal Infirmary, Bristol, UK, J. Bennett-Britton, J. Bewley, V. Bodenham, L. Cole, K. Driver, L. Grimmer, L. Howie, C. Searles, K. Sweet, D. Webster; Central Gippsland Health, Sale, VIC, A. van Berkel, H. Connor, J. Dennett, M. van Der Graaff; Christchurch Hospital, Christchurch, NZ, S. Henderson, J. Mehrtens, K. Miller, E. Minto, A. Morris, S. Noble, K. Parker; Dandenong Hospital, Melbourne, VIC, L. Bulfin, N. Hart, K. Shepherd, S. Vij; Derriford Hospital, Derriford, UK, S. Dickson, E. Elloway, C. Ferguson, R. Jackson, P. MacNaughton, M. Marner, R. Squire, S. Waddy, P. Wafer, J. Welbourne; Dorset County Hospital, Dorchester, UK, P. Ashcroft, D. Chambler, S. Dukes, A. Harris, S. Horton, S. Sharpe, P. Williams, S. Williams; Dunedin Hospital, Dunedin, NZ, M. Bailey, E. Blazquez, D. France, R. Hutchison, A. O'Connor; Gold Coast University Hospital, Gold Coast, QLD, G. Comadira, M. Gough, M. Tallott; Gosford Hospital, Gosford, NSW, M. Bastick, R. Cameron, S. Donovan, K. Ellis, A. Gaur, R. Gregory, J. Naumoff, E. Turner, M. White; Hornsby Ku-Ring-Gai Hospital, Sydney, NSW, KFJ. Au, J. Fratzia, S. Treloar; Hospital Pulau Pinang, Pulau Pinang, MY, CH. Lim, Maseeda.Y, AP. Tan, CL. Tang, CY. Yong; Inselspital Bern University Hospital, Bern, CH, M. Akaltan, S. Berger, D. Blaser, L. Fazlija, ML. Jong, M. Lensch, R. Ludwig, T. Merz, K. Nettelbeck, M. Roth, M. Schafer, J. Takala, A. Wehr, D. Zacharias; Institut Jantung Negara, Kuala Lumpur, MY, R. Amran, HN. Ashraf, N. Azmi, N. Basri, H. Burhanuddin, Y. Hadinata, A. Hamdan, S. Kadiman, AIYM. Rashid, IN. Sabran, S. Sulaiman, I. N. Zabidi; King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center, Riyadh, SA, A. Al-Dawood, M. Aljuaid, H. Al Anizi, A. Al Saeedi, Y. Arabi, M. Dbsawy, A. Deeb, M. Hegazy, I. Magdi; Kings College Hospital, London, UK, E. Clarey, E. Corcoran, C. Finney, C. Harris, P. Hopkins, H. Noble, J. Smith, L. Thompson, T. Williams ; King Saud Medical City, Riyadh, KSA, LA. Dumlao, R. Bassam, MA. Hassan, N. Naseem, MH. Al-Kurdi, AM. Al-Harthy; Knox Private Hospital, Melbourne, VIC, S. Bernard, L. Sebafundi, C. Serban; Kuala Lumpar General Hospital, Kuala Lumpur, MY, SK. Lim, N. Mazidah, N. Saidin, N. Sjamsuddin, ITA. Tan, N. Zabidi; Launceston General Hospital and Clifford Craig Medical Research Trust, Launceston, TAS, M. Brain, S. Mineall; Lyell McEwin Hospital, Adelaide, SA, M. Kanhere, N. Soar; Melaka General Hospital, Melaka, MY, N. Abd Kadir, NH. Abdullah, R. Awang, Z. Emperan, NS. Husin, NI. Ismail, SZ. Ismail, FNA. Mohd Khadzali, MF. Norddin; Middlemore Hospital, Auckland, NZ, J. Aguila, C. Bold, B. Clatworthy, A. Dias, C. Hogan, A. Kazemi, V. Lai, R. Song, A. Williams; Monash Medical Centre, Melbourne, VIC, D. Bhatia, L. Bulfin, S. Elliot, P. Galt, K. Lavrans, P. Ritchie, A. Wang; Nepean Hospital, Sydney, NSW, R. Gresham, J. Lowrey, K. Masters, P. Palejs, I. Seppelt, F. Symonds, L. Weisbrodt, C. Whitehead; Newcastle upon Tyne Hospitals (Freeman Hospital and Royal Victoria Infirmary), UK, M. Babio-Galan, V. Calder, I. Clement, A. Harrison, I. McCullagh, C. Scott, L. Thompson; North Shore Hospital, Auckland, NZ, R. Bevan, S. Caniba, D. Hacking, L. Maher; Ospedale San Raffaele, Milan, IT, ML. Azzolini, P. Beccaria, S. Colombo, G. Landoni, C. Leggieri, C. Luca, D. Mamo, E. Moizo, G. Monti, M. Mucci, A. Zangrillo; Prince of Wales, Sydney, NSW, M. Albania, S. Arora, Y. Shi; Prince Sultan Military Medical City, Riyadh, SA, A. Abudayah, G. Almekhlafi, E. Al Amodi, S. Al Samarrai, M. Badawi, R. Cubio Caba, O. Elffaki, Y. Mandourah, J. Valerio; Princess Alexandra Hospital, Brisbane, QLD, C.

Joyce, J. Meyer, E. Saylor, B. Venkatesh, E. Venz, J. Walsham, K. Wetzig; Princess Royal University Hospital, London, UK, E. Clarey, C. Harris, P. Hopkins, H. Noble, L. Thompson, T. Williams; Queen Elizabeth Hospital, MY, TM. Khoo, JES. Liew, AN. Sakthi, A. Zulkurnain; Queen Elizabeth Hospital Birmingham, Birmingham, UK, A. Bamford, C. Bergin, R. Carrera, L. Cooper, L. Despy, K. Ellis, S. Harkett, L. Mee, E. Reeves, C. Snelson, E. Spruce; Queen Elizabeth Hospital Kings Lynn, UK, G. Cooper, R. Hodgson, D. Pearson, M. Rosbergen; Raja Perempuan Zainab II Hospital, Kota Bharu, MY, MN. Ali, NI. Bahar, A. Ismail, WNW. Ismail, NM. Samat, NSM. Piah, R. Abd Rahman; Redcliffe Hospital, Brisbane, QLD, M. Duroux, M. Ratcliffe, T. Warhurst; Rotorua Hospital, Rotorua, NZ, U. Buehner, E. Williams; Royal Berkshire Hospital, Reading, UK, N. Jacques, L. Keating, S. Macgill, KL. Tamang, N. Tolan, A. Walden; Royal Bournemouth Hospital, Bournemouth, UK, R. Bower, J. Cranshaw, K. Molloy, S. Pitts; Royal Brisbane and Women's Hospital, Brisbane, QLD, J. Butler, R. Dunlop, C. Fourie, P. Jarrett, M. Lassig-Smith, A. Livermore, S. O'Donoghue, M. Reade, T. Starr, J. Stuart; Royal Darwin Hospital, Darwin, NT, L. Campbell, M. Phillips, D. Stephens, J. Thomas; Royal Hobart Hospital, Hobart, TAS, D. Cooper, R. McAllister; Royal Infirmary of Edinburgh, Scotland, UK, G. Andrew, L. Barclay, H. Dawson, DM. Griffith, D. Hope, G. Wojcik, C. McCulloch, R. Paterson; Royal Liverpool Hospital, Liverpool, UK, L. Ascough, C. Paisley, J. Patrick-Heselton, D. Shaw, V. Waugh, K. Williams, I. Welters; Royal Melbourne Hospital, Melbourne, VIC, D. Barge, A. Jordan, C. MacIsaac, T. Rechnitzer; Royal North Shore Hospital, Sydney, NSW, F. Bass, J. Gatward, N. Hammond, P. Janin, A. O'Connor, W. Stedman, E. Yarad; Sarawak General Hospital, Sarawak, MY, NA. Razak, N. Dzulkipli, SL. Jong, K. Asen, WL. Voon, S. Liew; St George's Hospital London, UK, J. Ball, V. Barnes, C. Dalton, S. Farnell-Ward, H. Farrah, K. Maher, J. Mellinghoff, C. Ryan, P. Shirley; St James University Hospital, Dublin, IR, L. Conlon, A. Glover, I. Martin-Loeches, E. O'Toole; St John of God Hospital Subiaco, Subiaco, WA, J. Ewan, J. Ferrier, E. Litton, SA. Webb; St Thomas Hospital, London, UK, , W. Berry, U. Blanco Alonso, A. Bociek, S. Campos, S. Jawara, F. Hanks, A. Kelly, K. Lei, C. McKenzie, M. Ostermann, R. Wan, St Vincent's Hospital, Sydney, NSW, S. Al-Soufi, S. Leow, K. McCann, C. Reynolds; St Vincent's University Hospital, Dublin, IR, K. Brickell, C. Fahey, L. Hays, N. Hyde, A. Nichol, D. Ryan; Sunshine Coast University Hospital and Nambour Hospital, Sunshine Coast, QLD, J. Brailsford, A. Buckley, L. Forbes, T. Maguire, J. Moore, L. Murray; The Northern Hospital, Melbourne, VIC, A. Ghosh, M. Park, S. Said; Toowoomba Hospital, Toowoomba, QLD, J. Smith, A. Visser; Universiti Sains Malaysia Hospital, MY, HZ. Abidin, S. Ali, MH. Hassan, SC. Omar, WFW. Shukeri; University College Hospital London, UK, D. Brealey, G. Bercades, E. Blackburn, N. Macallum, A. Macklin, JH. Ryu, K. Tam, D. Smyth; University Hospital of Coventry and Warwick, Coventry, UK, A. Arif, C. Bassford, C. Morgan, C. Swann, G. Ward, L. Wild; University Hospital Geelong, Geelong, VIC, A. Bone, T. Elderkin, D. Green, D. Sach, T. Salerno, N. Simpson; University Hospital of North Tees, Stockton-on-Tees, UK, F. Brohi, M. Clark, L. Williams; University Hospital of Wales, Cardiff, UK, J. Brooks, E. Cocks, J. Cole, J. Curtin, R. Davies, H. Hill, M. Morgan, N. Palmer, C. Whitton, M. Wise; University Malaya Medical Center, MY, P. Baskaran, MS. Hasan, LY. Tham; Wellington Regional Hospital, Wellington, NZ, R. Sol Cruz, D. Dinsdale, S. Edney, C. Firkin, F. FitzJohn, G. Hill, A. Hunt, S. Hurford, G. Jones, H. Judd, C. Latimer-Bell, C. Lawrence, E. Lesona, L. Navarra, Y. Robertson, H. Smellie, AM. Vucago, P. Young; Western General Hospital Scotland, Edinburgh, UK, H. Dawson, DM. Griffith, R. Paterson; Westmead Hospital, Sydney, NSW, P. Clark, J. Kong, J. Ho, V. Nayyar, C. Skelly.