

1 THE IMPORTANCE OF BEING THE MORNING CASE IN ADULT CARDIAC SURGERY:
2 A PROPENSITY-MATCHED ANALYSIS

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23 Key question: Does the timing of surgery have any effect on the outcome of the patients?
24 Key findings: Patients operated in the afternoon had a higher 30-days mortality and
25 morbidity rate.
26 Take-home messages: Second-case patients are exposed to a worse outcome likely due
27 to fatigue and hurriedness in the Operating Room and in the Intensive Care.

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28 Abstract

29 *Objectives:* The quality of the outcome after cardiac surgery with cardiopulmonary bypass
30 depends on the patient demographics, co-morbidities, complexity of the surgical
31 procedure, and expertise of surgeons and the whole staff. The purpose of the present
32 study is to analyze the timing of surgery (morning vs. afternoon) with respect to morbidity
33 and mortality in adult cardiac surgery. *Methods:* The primary endpoint was the incidence of
34 major morbidity defined according to a modified Society of Thoracic Surgeon criterion. We
35 consecutively included all the adult (> 18 years) patients receiving a cardiac surgery
36 operation at our Institution.

37 *Results:* From 2017 through 2019 a total of 4,003 cardiac surgery patients were operated.
38 With a propensity-matching technique a final patient population of 1600 patients was
39 selected, with 800 patients in the first-case surgery group and 800 in the second-case
40 surgery group. Patients in the second-case group had a major morbidity rate of 13% vs
41 8.8% in the first-case group (P=0.006), and a higher rate of 30-days mortality (4.1% vs.
42 2.3%, P=0.033). After correction for EuroSCORE and operating surgeon, the second-case
43 group confirmed a higher rate of major morbidity (odds ratio 1.610, 95% confidence
44 interval 1.16-2.23, P=0.004). *Conclusion:* Our study suggests that patients operated as
45 second cases are exposed to an increased morbidity and mortality probably due to fatigue,
46 loss of attention and hurriedness in the operating room, and decreased human resources
47 in the intensive care unit.

48

49 **Keywords:** morbidity; mortality; outcome; daytime variation; cardiac surgery.

50 Abbreviations

51	ASMD	Absolute Standardized Mean Difference
52	CPB	Cardiopulmonary Bypass
53	EC	Ethical Committee
54	HCT	Hematocrit
55	ICU	Intensive Care Unit
56	LCOS	Low Cardiac Output State

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57 Introduction

58 The outcome after a cardiac surgery operation with cardiopulmonary bypass (CPB)
59 depends on a number of factors. Some are related to patient's demographics and co-
60 morbidities. Others depend on the nature and complexity of the surgical procedure.
61 Besides these factors, the technical skill and expertise of surgeons, anesthesiologists,
62 perfusionists, intensivists, and nurses, is of paramount importance.
63 The quality of the human performance is in turn dependent on other factors, like fatigue,
64 decreased attention, sleep deprivation, stress [1]. Hospital admission during the night
65 hours or the weekend has been associated with a worse outcome, and this has been
66 attributed to a lower skill of the attending clinicians [2,3]. In some non-cardiac surgeries,
67 postoperative morbidity and mortality was higher in patients operated in the afternoon or
68 nighttime [4-6], and anesthesia-linked adverse events are more frequent in cases operated
69 after 4 p.m. [7].
70 Many authors addressed the timing of cardiac surgery (morning vs. afternoon) in order to
71 investigate if this had an impact in terms of postoperative morbidity and mortality.
72 There are studies where no differences were found [8-14], and others where there was a
73 clear trend towards a higher mortality rate in the afternoon cases, however not reaching a
74 statistical significance due to an inadequate power of the sample size [15,16]. Other
75 authors found different results, showing a clear increase in morbidity and mortality for the
76 afternoon cases [17,18].
77 In this controversial scenario, that is of course based on retrospective analyses, the great
78 majority of the studies suffer from some sources of bias. Among these, the most important
79 are the non-consideration of the operating surgeon expertise; the inclusion of low-risk
80 patients only; and a disproportion in the sample size of the two groups (usually,
81 considerably larger in the morning group).

82 The purpose of the present study is to analyze the timing of surgery with respect to
83 morbidity and mortality, with a propensity-matched analysis, and the inclusion of many
84 items that were underestimated in the previous studies.

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86 Methods

87 This is a retrospective, propensity-matched study. The study was monocentric, conducted
88 at the IRCCS Policlinico San Donato, a Clinical Research Hospital partially funded by the
89 Italian Ministry of Health.

90 The primary endpoint was the incidence of major morbidity defined according to a modified
91 Society of Thoracic Surgeon definition [19] as surgical re-operation, stroke, acute kidney
92 injury, sepsis (instead of deep wound infection), or mechanical ventilation > 48 hours.
93 Secondary endpoints included mortality at 30 days, low cardiac output state, duration of
94 mechanical ventilation and ICU (Intensive Care Unit) and postoperative hospital stay.

95 *Ethics statement*

96 The study was approved by the local Ethics Committee (EC, IRCCS San Raffaele
97 Hospital). The approval number is 119/INT/2022, the approval date October 12, 2022.
98 Given the retrospective nature of the study, a specific written informed consent was
99 obtained whenever feasible; the remaining patient population gave a written informed
100 consent for the use of their clinical data in an anonymous form, and for scientific purposes.

101 *Patient population*

102 We included all the adult (> 18 years) patients receiving a cardiac surgery operation with
103 CPB at our Institution from 2017 to 2019. Exclusion criteria were: congenital heart disease
104 and emergency cases. We excluded from the analysis the patients operated by surgeons
105 with a minimal level of activity (< 20 cases in the study period).

106 *Data collection and definitions*

107 All data were retrieved from our institutional database. This included demographics, co-
108 morbidities (defined according to the EuroSCORE II) [20], surgical details, and outcome.
109 Mortality was considered at 30-days from surgery. Risk stratification was achieved
110 according to the EuroSCORE II. EuroSCORE II predicts hospital mortality: according to

111 the data published by the authors, we applied a modified EuroSCORE II for 30-days
112 mortality, by adding 0.6% [20].
113 The morbidity events were defined as follows: acute kidney injury was adjudicated for a
114 serum creatinine increase of 100% with respect to baseline; sepsis as systemic infection
115 confirmed by blood cultures; stroke as central nervous damage confirmed by imaging.
116 Low cardiac output state (LCOS) was adjudicated in case of need for inotropic drugs > 48
117 hours.

118 Additional items included a complete metabolic profile of the patient immediately at the
119 ICU admission, with arterial blood gas analysis (inclusive of acid-base balance, arterial
120 oxygen tension, inspiratory oxygen fraction, and arterial blood lactates), hematocrit (HCT,
121 %), systemic arterial pressure (mmHg), central venous pressure (mmHg), heart rate
122 (beats/min), central temperature (°C)

123 First case group comprised patients operated in the morning (induction of anesthesia at
124 8.00 a.m.) and second case group patients operated after the first case (induction of
125 anesthesia between 12 a.m. and 5.00 p.m. (last timing applied in our Institution for
126 initiating non-emergency cases).

127 *Sample size and statistics*

128 The sample size was settled based on the primary endpoint (difference in major morbidity).
129 From a retrospective analysis of our database, the incidence of major morbidity was 12%.
130 We hypothesized that the second vs. first case had a 50% difference, i.e., first case 9%
131 and second case 14%. Based on this hypothesis, and with an alpha value of 0.05 and a
132 power of 80%, the sample size was settled at 1,236 patients (638 in each group).

133 The propensity matching process followed the current state of the art [21,22]. Basically, we
134 performed a logistic regression model fitted with timing of surgery (first vs. second case)
135 as the dependent variable; explanatory variables suspected of being confounders had to
136 fulfil these categories: (i) occur temporarily before the outcome measure; (ii) are

137 associated with the timing of surgery; and (iii) are associated with the outcome at a level of
138 absolute standardized mean difference (ASMD) > 0.10.

139 The correct matching was checked through an analysis of the ASMD after matching.

140 According to the current standards, an ASMD < 0.15 is considered a very small effect size,
141 and between 0.15 and 0.20 a small effect size [23]. Given the large sample size, a very
142 sensitive threshold for imbalance was settled at <0.10.

143 All data are expressed as number (%) or mean (standard deviation) and median
144 (interquartile range) depending on the normality of distribution. Differences between
145 percentages have been tested with a Pearson's chi squared; differences between
146 continuous variables have been tested with a Student's t test or non-parametric tests as
147 appropriate. For differences between means, the mean difference with 95% confidence
148 interval was indicated. A logistic regression analysis was applied in the sensitivity analysis,
149 producing odds ratios and 95% confidence intervals. We estimated the associations and
150 the odds ratio between timing of surgery and postoperative outcome after matching, using
151 logistic regression models with robust standard errors. All the statistical analyses were
152 performed with computerized packages (SPSS 20.0, IBM, Chicago, IL, GraphPad,
153 GraphPad Software, Inc, San Diego, CA, SAS version 9.4, SAS Institute, Inc., Cary, NC,
154 and MedCalc, MedCalc Software, Ostend, Belgium). A two-tailed P value < 0.05 was
155 considered significant for all the statistical tests.

156

157 Results

158 From January 2017 through December 2019 a total of 4,003 cardiac surgery patients were
159 operated at our Institution. Figure 1 shows the flowchart leading to our final patient
160 population. After exclusion of congenital heart patients (N=1,384), emergency/salvage
161 cases (N=54), and surgeons with a minimal (< 20 cases in 3 years) level of activity (N=60),
162 2,505 patients remained available for the analyses; 1,458 patients belonged to the first
163 case group, and 1,047 to the second case group.

164 In Table 1 we have reported the details of patients in the first and second case group
165 before and after matching. Before matching, the absolute standardized mean difference
166 exceeded the limit of ± 0.10 for a number of variables: left ventricular ejection fraction,
167 serum creatinine, serum bilirubin, congestive heart failure, active endocarditis, previous
168 cerebrovascular accident, redo surgery, non-elective surgery, CPB duration, aortic cross
169 clamp time, nadir temperature on CPB, and operating surgeon. We did apply a logistic
170 regression including these variables as independent variables, and the timing of surgery
171 (first vs. second case) as dependent variable. The propensity-score matching required the
172 elimination of 247 patients from the second case group, due to impossible matching with
173 similar propensity scores patients in the first case group. The final patient population was
174 800 patients in the second case group, that were matched at a 1:1 ratio (without
175 replacement) with patients of the first case group. This final patient population largely
176 exceeded the minimal sample size required to verify our hypothesis. After matching, the
177 ASMD remained always < 0.10 , thus demonstrating a minimal between groups difference.
178 Table 2 and figure 2 report the outcome of the two groups. Patients in the second case
179 group had a significantly ($P=0.002$) higher rate of major morbidity, and a significantly
180 higher rate of 30-days mortality ($P=0.005$). Within the components of major morbidity,
181 sepsis and mechanical ventilation > 48 hours had a significantly ($P=0.010$ and $p=0.032$,
182 respectively) higher rate in the second case group. The rate of early ($6 <$ hours) extubation

183 was significantly ($P < 0.0001$) lower in the second case group, and the LCOS rate was
184 significantly ($P = 0.003$) higher in the second case group. No other outcome differences
185 were noticed. The early extubated patients in the second case group received a nocturnal
186 extubation. Within the second case group, those receiving nocturnal extubation (66
187 patients) had no significant morbidity and mortality differences with respect to patients
188 extubated ≥ 6 hours. We conducted a more specific analysis of the 30-day mortality within
189 the second case group, to identify whether the timing of surgery was associated with the
190 outcome. Figure 3 shows the cubic spline function obtained in the interval between 12 AM
191 and 5 PM. No specific trend was identified, and, within the second case group, an early or
192 late beginning of surgery was not associated with differences in mortality.

193 At the arrival in the ICU the second case group had a significantly higher arterial blood
194 lactate level (1.92 ± 1.97 mMol/L vs. 1.64 ± 1.16 mMol/L, $P = 0.001$) and a larger proportion of
195 patients with arterial blood lactates > 3 mMol/L (12.6% vs. 7.6%, $P = 0.001$), with a trend
196 towards a lower pH (7.38 ± 0.13 vs. 7.40 ± 0.06 , $P = 0.017$).

197 A sensitivity analysis was conducted to better investigate the role of timing of surgery
198 within the context of predicted mortality rate, operating surgeon and attending
199 anesthesiologist. For this last item, given the considerable turn-around in the four years
200 period (30 different anesthesiologists), the analysis was conducted for expertise classes,
201 considering a class 1 (> 10 years of clinical practice), class 2 (3-10 years of clinical
202 practice), and class 3 (< 3 years of clinical practice) stratification. There were no significant
203 differences in the distribution of expertise classes between morning and afternoon case:
204 Class 1 anesthesiologists attended 44.2% of the cases (43.7% morning cases and 44.7%
205 afternoon cases); class 2 anesthesiologists attended 16.3% of the cases (16.5% morning
206 cases and 16.1% afternoon cases), and class 3 anesthesiologists attended 39.5% of the
207 cases (39.8% morning cases and 39.2% afternoon cases), for an overall P value of 0.917.
208 Table 3 reports the results of this sensitivity analysis. Overall, the total observed mortality

209 rate was lower than the predicted value according to the EuroSCORE II. Six surgeons had
210 a significantly lower mortality rate than expected, three - a mortality rate equivalent to the
211 expected, and one - a mortality rate higher than expected. A multivariable logistic
212 regression analysis confirmed that after correction for the EuroSCORE II and the operating
213 surgeon, the second case of the day carries a 61% higher major morbidity risk and a 2-fold
214 mortality risk with respect to the first case.

215 When the second case was performed by the same surgeon of the first case (this applies
216 to the two surgeons with the highest level of activity, with 844 cases, 53% of the total
217 activity), the logistic regression analysis showed that after correction for surgeon and
218 EuroSCORE II, the major morbidity risk increased for the second case reaching an odds
219 ratio of 2.1 (95% confidence interval 1.3-3.2, $P=0.001$) whereas mortality decreased to an
220 odds ratio of 1.85 (95% confidence interval 0.91-3.7, $P=0.088$).

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222 Discussion

223 Our study demonstrates that, once adjusted for the potential confounders, the second
224 cardiac surgery case of the day carries a 60% higher risk of major morbidity and twice the
225 risk of 30-days mortality. The main determinants of this worse outcomes are LCOS and
226 infections, leading to prolonged mechanical ventilation and ICU stay. At the arrival in the
227 ICU, the second case group has a larger rate of hyperlactatemia.

228 When the analysis was restricted to surgeons operating the first and second case on the
229 same day, the risk of major morbidity for the second case was double the risk for the first
230 case.

231 *The evidence of confounding factors*

232 We think that a preliminary consideration should be deserved to the pre-matching
233 differences between groups. Table 1 clearly shows an impressive number differences, that
234 certainly represent potential sources of bias when addressing the outcome data. In
235 general, the second case carries a higher preoperative risk, that is however basically a
236 patient-dependent risk plus a larger rate of redo and non-elective procedures. The type of
237 operation is basically well balanced between first and second case, whereas there is an
238 imbalance in the operating surgeon, with the most experienced surgeons mainly operating
239 the first case. This is probably reflected by the longer CPB and aortic cross-clamp times,
240 that however reflect even the larger rate of redo cases.

241 It is the policy of our Institution (and probably of others), when a senior surgeon has two
242 cases scheduled on the same day, to place the most demanding case as second case.

243 This is basically due to the need of operating without the burden of a second waiting case
244 who, in case of prolongation of the first one, suffers the risk of being postponed to the
245 following day.

246 Overall, the presence of so many patient-related and surgeon-related confounders,
247 requires adequate statistical procedures to assess comparable groups. The propensity-

248 matching provided us with two groups where only the timing of surgery was the
249 independent variable, all the others being homogeneous. Additionally, given the
250 paramount importance of risk stratification (EuroSCORE II) and of the operating surgeon,
251 we conducted a sensitivity analysis which was confirmative of the general results. Within
252 this analysis, when the surgeon operating the second case is the same of the first case,
253 the major morbidity risk increases.

254 All these considerations are necessary when analyzing the previous studies published on
255 this topic. Although the majority of the studies addressed the problem of confounders with
256 a propensity-matched approach [8-10,14-16, 24], others did not [17, 18, 25, 26]. Few
257 studies included the operating surgeon within the possible confounders [12,15,18], and no
258 study investigated whether the second case was done by the first surgeon operating the
259 first case. This last factor is of particular importance, once the possible role of fatigue is
260 advocated as a determinant of different outcomes.

261 *The major morbidity and mortality outcome*

262 The majority of the studies [8-10,12-16, 25, 26] found no differences between morning and
263 afternoon surgery in terms of morbidity and mortality, one [24] found a better outcome for
264 the afternoon cases, and others [17,18], in agreement with our results, for the morning
265 cases.

266 Montaigne and associates [24] in a propensity-matched series of 596 cardiac surgery
267 patients, found more major adverse events in the morning case group; however, they
268 selected a population at low predicted mortality risk (EuroSCORE II 1.8%), and restricted
269 their analysis to aortic valve replacement due to stenosis, in patients with preserved left
270 ventricular ejection fraction. Heller and associates [8] compare 248 morning cases to 124
271 night cases, founding no differences in morbidity and mortality. However, even after
272 propensity matching, the nighttime group had a lower operative risk, with significantly
273 shorter anesthesia and cardiopulmonary bypass time. Hijazi and associates [9] compared

274 two large groups of morning and afternoon cases, adjusting for confounders with a logistic
275 regression analysis, and found no differences in morbidity and mortality. However, in
276 procedures at high risk (aortic valve replacement + coronary surgery + other procedure),
277 the afternoon group had a mortality rate of 5.4% vs. 1.6% for the morning group. In a large
278 patient population (> 3,000 cases) propensity matched, Bianco and associates [10] found
279 no differences in morbidity/mortality rate. Another large size (2,720 cases) study, Götte
280 and associates [12] found no differences in outcome between the morning and the
281 afternoon cases; however, they restricted their population to isolated aortic valve
282 replacement or aortic valve replacement + coronary surgery. A similar patient selection
283 can be found in the study of Nemeth and associates [13] who did not find any
284 morbidity/mortality difference between morning and afternoon cases, in patients receiving
285 isolated coronary or aortic valve surgery. In this study, the deep sternal wound infection
286 was however double in the afternoon cases (P=0.054). Axtell and associates [14] excluded
287 mitral valve surgery, combined operations, redo surgery. Of interest, in this last study, the
288 afternoon case had again a significantly (P=0.02) higher risk of deep sternal wound
289 infection (odds ratio 8.3).

290 Kenney and associates [15] explored a Danish registry and compared about 1,400
291 propensity matched morning vs. afternoon cases. They did not found differences in
292 mortality, although it was double in the afternoon group, nor in morbidity. However, the
293 mechanical ventilation time was significantly longer in the afternoon group. Similar results
294 are shown by Baik and associates [16], with a mortality rate of 2.7% in the afternoon group
295 vs. 1.5% in the morning group (P=0.259). Coumbe and associates [17] found a higher
296 mortality rate (6.2%) in patients operated after 4 p.m. than before (2.2%). However, the
297 two groups were not matched (2,624 vs. 65 cases), with a higher rate of urgent/emergent
298 surgery in the late case group. Finally, in a model accounting for the operating surgeon,

299 Yount and associates [18] found a 2x higher absolute and risk-adjusted mortality in
300 patients operated after 3 p.m.
301 In this rather confused scenario, our study has the strengths of a 1:1 propensity matching
302 with relatively large sample size; of the inclusion of the operating surgeons as potential
303 confounders accounted for in the propensity matching process and adjusted for in the
304 sensitivity analyses; the identification of afternoon cases done by the same surgeon of the
305 first case; and finally, the exclusion of emergency cases only. Additionally, we could collect
306 data that were not considered in other studies, and that may be useful for understanding
307 the source of the worse morbidity/mortality outcome found in the second case group in our
308 study.

309 *Where does the problem occur?*

310 The analysis of data at the admission in the ICU offers useful insights to understand the
311 nature of the problem(s) underlying the worse outcome of the second cases. Despite a
312 similar type of surgery, and no differences in CPB time, aortic cross-clamp time, level of
313 hypothermia on CPB, the second case reaches the ICU with a higher lactate level, and
314 with a higher rate of hyperlactatemia. Early hyperlactatemia is associated with morbidity
315 and mortality after cardiac surgery [27] and is generally associated with LCOS. In our
316 series, the second case group showed a higher rate of LCOS. Given the early pattern of
317 hyperlactatemia, it is likely that it initiated during the late phases of surgery, after
318 discontinuation from CPB. These phases, in the second surgical cases, occur quite late in
319 the evening or even during nighttime. Our hypothesis is that the surgical team (and namely
320 the anesthesiologist) could have underestimated the early signs of a LCOS, due to a
321 combination of fatigue and willingness to reach the ICU and leave the care of the patient to
322 the intensivist. This hypothesis was already raised by Yount and associates [18] who
323 noticed that *“physicians are more motivated to accomplish tasks at the end of a day or
324 week to avoid after-hours care”*. This hurriedness could be responsible even for another

325 finding that our study shares with other previous studies [13,14,18], that is higher rate of
326 infections in the second or afternoon case. One possible interpretation could be that the
327 multiple shift changes (anesthesia nurse and scrub nurse) occurring between the first and
328 second case increases the “traffic” in the operating room, and therefore the risk of
329 infection. Additionally, a less cautious observation of asepsis rules in medication and
330 patient manipulation and transfer could be a possible mechanism.

331 All these hypotheses related to operating room dependent factors are probably not enough
332 to justify the worse outcome of the second case. Other factors, probably linked to the late
333 arrival in the ICU, are probably playing a role. The first 6 postoperative hours, often
334 referred to as the “golden hours”, are nocturnal hours in the ICU for the second case.
335 Overnight, the physician/patient ratio is considerably reduced at our Institution. Basically, it
336 is 4 or 5 doctors for 26 beds during daytime, and 2 doctors only (plus other 2 on call) at
337 night. Additionally, during daytime all the staff is composed by intensivists and/or
338 anesthesiologists, whereas overnight there is one cardiac surgeon and one
339 anesthesiologist/intensivist. Under these circumstances, the overnight activities must take
340 into account the reduced physician/patient ratio. Early extubation was only 8% overnight
341 (25% during daytime), leading to prolonged mechanical ventilation and ICU stay.
342 Mechanical ventilation represents *per se* a factor favoring respirator and manipulation-
343 induced infections.

344 Overall, it is not easy to extrapolate the events or sequence of events leading to the worse
345 outcome of the second cardiac surgery case. The chain of events certainly starts in the
346 operating room and proceeds in the early hours after admission to the ICU, and the human
347 factor is the main issue. Fatigue and loss of attention are the usual suspects, and their
348 effect on the performance and the errors in the medical setting are well established [1].

349 Different authors hypothesized the role of nocturnal extubation as determinant of bad
350 outcomes, with different conclusions. In our series, only 8% of the patients had a nocturnal
351 extubation and they did not show morbidity or mortality differences.

352 Finally, other authors pointed out a possible role of circadian rhythms as determinants of
353 different outcomes between morning and afternoon surgery. The only author showing a
354 superiority of afternoon surgery [24] suggested that the factors usually increasing cardiac
355 events in the early morning may favor bad outcomes in morning cardiac surgery.

356 There are limitations in our study. The main is that we could not include in the analysis the
357 possible role of the intensivist and the perfusionist as possible confounding factors.

358 The already mentioned strengths are the inclusion of the operating surgeon in the
359 propensity matching, the analysis restricted to surgeons doing both the first and the
360 second case, and the inclusion of data at the arrival in the ICU.

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362 Conclusion

363 Our study shows that the second cardiac surgery case has a worse outcome, regardless
364 of the patient profile and complexity of the procedure. This suggests that it is not wise to
365 place the most demanding cases as second cases, when they are exposed to an
366 increased morbidity and mortality due to fatigue, loss of attention and hurriedness in the
367 operating room, and decreased human resources in the ICU. These findings have been
368 discussed internally at our Institution, and efforts are presently applied to avoid treating
369 very difficult patients as second cases.

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371 Data Availability

372 The original dataset supporting the findings of this study will be deposited in the public
373 repository Zenodo and accessible upon a reasonable request.

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377 Italian Ministry of Health.

378 Conflict of interest

379 The authors declare no Conflict of Interest with respect to the present work.

380 Author contribution

381 MR designed the study, analyzed and interpreted the data and wrote the manuscript.

382 SC designed the study, helped acquiring the data, interpreted the data and wrote the
383 manuscript. AF, MD, AP, LM, CDV helped acquiring the data and critically revised the
384 manuscript. SB revised and extended the statistical analysis.

385 All the authors gave their final approval to the version to be published.

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392 Figure legend

393 Figure 1

394 Flowchart leading to the final patient population.

395 Figure 2

396 Comparison of the outcome between the two groups

397 Figure 3

398 Cubic spline function of the association between the initial hour of anesthesia induction
399 and 30-day mortality within the second case group. Dashed lines are 95% confidence
400 interval. The blue dot is the mortality rate (with 95% confidence interval of the first case
401 group.

402 Central image: Comparison of the outcome between the two groups

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405 Table 1. Pre- and intraoperative variables before and after matching

407 Variable	408 First case (N=1,458)	409 Second case (N=1,047)	410 ASMD pre-match	411 First case post-match (N=800)	412 Second case post-match (N=800)	413 ASMD post-match
411 Age (years)	66.6 (12.7)	67.3 (12.5)	- 0.05	67.2 (12.5)	66.7 (12.6)	0.04
412 Weight (kgs)	73.4 (14.9)	73,8 (15.6)	- 0.02	73 (14.5)	74.1 (15.7)	- 0.07
413 Gender male	923 (63.3)	686 (65.5)	- 0.06	503 (62.9)	527 (65.9)	- 0.06
414 Ejection fraction (%)	55.1 (11.6)	53.7 (11.8)	0.11	55.1 (11.5)	54.3 (11.6)	0.07
415 Serum creatinine (mg/dL)	1.05 (0.70)	1.14 (1.01)	- 0.11	1.09 (0.80)	1.12 (1.04)	- 0.03
416 Serum bilirubin (mg/dL)	0.64 (0.30)	0.68 (0.39)	- 0.11	0.65 (0.29)	0.67 (0.39)	- 0.06
417 Preoperative hematocrit (%)	40.2 (11.3)	39.5 (9.3)	0.07	40.3 (14.8)	39.9 (10.1)	0.03
418 Diabetes on medication	246 (17)	187 (18)	- 0.03	143 (18)	137 (17)	0.03
419 COPD	34 (2.3)	24 (2.3)	0.00	22 (2.8)	14 (1.8)	0.07
420 Congestive heart failure	102 (7.0)	109 (10.4)	- 0.12	59 (7.4)	66 (8.3)	- 0.03
421 Active endocarditis	30 (2.1)	45 (4.3)	- 0.13	25 (3.1)	26 (3.3)	- 0.01
422 Previous CVA	39 (2.7)	53 (5.1)	- 0.12	29 (3.6)	32 (4.0)	- 0.02
423 Isolated CABG	318 (21.8)	352 (24.1)	- 0.05	185 (23.1)	188 (23.5)	- 0.01
424 Isolated aortic valve surgery	328 (22.5)	203 (19.4)	0.08	163 (20.4)	163 (20.4)	0
425 Isolated mitral valve surgery	260 (17.8)	200 (19.1)	- 0.03	141 (17.6)	166 (20.8)	- 0.08
426 Ascending aorta surgery	106 (7.3)	83 (7.9)	- 0.02	67 (8.4)	60 (7.5)	0.03
427 Combined surgery	495 (34)	375 (35.8)	- 0.04	281 (35.1)	274 (34.3)	0.02
428 Others	63 (4.3)	34 (3.2)	0.06	31 (3.9)	24 (3.0)	0.05
429 Redo surgery	95 (6.5)	99 (9.5)	- 0.11	62 (7.8)	64 (8.0)	- 0.01
430 Non-elective surgery	236 (16.2)	290 (27.7)	- 0.28	182 (22.8)	176 (22)	0.02
431 EuroSCORE II	3.4 (3.2)	4.3 (4.8)	- 0.22	3.8 (3.7)	3.7 (3.6)	0.03
432 CPB time (min)	85 (36)	104 (54)	- 0.41	93 (40)	96 (45)	- 0.07
433 Aortic X-clamp time (min)	63 (27)	74 (36)	- 0.35	68 (30)	70 (33)	- 0.06
434 Nadir T on CPB (°C)	33 (2.8)	32.7 (2.2)	0.12	33 (3.5)	32.8 (2.1)	0.07

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Table 1 (continued)

Variable	First case (N=1,458)	Second case (N=1,047)	ASMD pre-match	First case post-match (N=800)	Second case post-match (N=800)	ASMD post-match
Surgeon						
A (junior)	67 (4.6)	113 (10.8)	- 0.23	64 (8.0)	65 (8.1)	0
B (senior)	84 (5.8)	132 (12.6)	- 0.24	80 (10)	72 (9.0)	0.03
C (head of department))	492 (33.7)	260 (24.8)	0.21	240 (30)	230 (28.7)	0.03
D (senior)	30 (2.1)	34 (3.2)	- 0.07	23 (2.9)	34 (4.3)	- 0.07
E (senior)	13 (0.9)	29 (2.8)	- 0.14	11 (1.4)	15 (1.9)	- 0.04
F (senior)	72 (4.9)	57 (5.4)	- 0.02	44 (5.5)	49 (6.1)	- 0.03
G (junior)	38 (2.6)	79 (7.5)	- 0.22	37 (4.6)	45 (5.6)	- 0.04
H (director)	520 (36)	209 (20)	0.36	180 (22.5)	194 (24.3)	- 0.04
I (senior)	79 (5.4)	103 (9.8)	- 0.17	76 (9.5)	66 (8.2)	0.05
J (senior)	63 (4.3)	31 (3.0)	0.07	45 (5.6)	30 (3.7)	0.09

Data are mean (standard deviation) or number (%). ASMD: absolute standardized mean difference; CABG: coronary artery bypass graft; COPD (chronic obstructive pulmonary disease; CPB: cardiopulmonary bypass; CVA: cerebrovascular accident; T: temperature.
° Corrected for 30-days mortality.

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462 Table 2. Postoperative outcome

465 Item	466 First case N = 800	467 Second case N=800	468 O.R. (95% C.I.)	469 P
470 30-days mortality	471 18 (2.3)	472 33 (4.1)	473 1.81 (1.20-2.73)	474 0.005
475 Major Morbidity	476 70 (8.8)	477 104 (13)	478 1.56 (1.18-2.07)	479 0.002
480 Acute kidney injury	481 14 (1.8)	482 23 (2.9)	483 1.66 (0.88-3.13)	484 0.116
485 Stroke	486 11 (1.4)	487 7 (0.9)	488 0.63 (0.25-1.58)	489 0.326
490 Sepsis	491 12 (1.5)	492 29 (3.6)	493 2.47 (1.25-4.89)	494 0.010
495 Surgical revision	500 29 (3.6)	501 36 (4.5)	502 1.25 (0.89-1.76)	503 0.191
504 Mechanical ventilation > 48 hours	505 30 (3.8)	506 54 (6.8)	507 1.86 (1.05-3.28)	508 0.032
509 Inotropic drugs > 48 hours	510 92 (11.5)	511 134 (16.8)	512 1.55 (1.17-2.06)	513 0.003
514 Mechanical ventilation time (hours)	515 16 (6-18)	516 13 (11-17)	517 1.00 (0.99-1.00)	518 0.097
519 Early (< 6 hours) extubation	520 206 (25.8)	521 66 (8.3)	522 0.26 (0.20-0.33)	523 <0.0001
524 ICU stay (days)	525 1 (1-3)	526 1 (1-3)	527 1.01 (1.00-1.03)	528 0.067
529 Postoperative hospital stay (days)	530 8 (7-11)	531 8 (7-11)	532 1.01 (1.00-1.02)	533 0.244

493 Data are median (interquartile range) or number (%). ICU: intensive care unit

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496 Table 3. 30-days mortality sensitivity analysis

499 Surgeon	500 Predicted mortality° (%, 95% CI)	500 Observed mortality (%, 95% CI)	500 Observed vs. predicted (significant at a P value <0.05)
503 A	3.1 (2.7-3.6)	0.8 (0-2.3)	Significantly lower
504 B	3.3 (2.9-3.7)	2.6 (0-5.2)	Equivalent
505 C	4.3 (3.9-4.7)	4.0 (2.2-5.8)	Equivalent
506 D	2.9 (2.2-3.5)	1.7 (0-5.3)	Significantly lower
507 E	2.9 (2.1-3.7)	3.8 (0-11.7)	Significantly higher
508 F	2.9 (2.4-3.4)	2.1 (0-5.2)	Significantly lower
509 G	3.6 (2.8-4.4)	1.2 (0-3.7)	Significantly lower
510 H	4.2 (3.8-4.8)	4.8 (2.6-7.0)	Equivalent
511 I	3.1 (2.7-3.4)	2.1 (0-4.5)	Significantly lower
512 J	2.8 (2.3-3.2)	1.3 (0-3.9)	Significantly lower
513 Total	3.7 (3.6-3.9)	3.2 (2.3-4.0)	Significantly lower

515 Multivariable major morbidity analysis – all surgeons

519 Factor	519 Regression coefficient	519 Odds Ratio (95% CI)	519 P
521 Surgeon	- 0.005	0.996 (0.98-1.01)	0.553
522 Anesthesiologist expertise class	- 0.108	0.897 (0.75-1.05)	0.240
523 EuroSCORE II°	0.118	1.125 (1.09-1.16)	0.001
524 Second vs. first case	0.476	1.610 (1.16-2.23)	0.004
525 Constant	- 2.807		

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531 Table 3 – continued

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533 Multivariable 30-days mortality analysis – all surgeons

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535 Factor	Regression coefficient	Odds Ratio (95% CI)	P
537 Surgeon	0.005	1.005 (0.98-1.03)	0.695
538 Anesthesiologist expertise class	- 0.247	0.781 (0.57-1.07)	0.130
539 EuroSCORE II ^o	0.126	1.134 (1.08-1.18)	0.001
540 Second vs. first case	0.663	1.940 (1.07-3.52)	0.029
541 Constant	- 4.449		

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544 Multivariable major morbidity analysis – surgeons operating both first and second case

545

546 Factor	Regression coefficient	Odds Ratio (95% CI)	P
548 Surgeon	0.001	1.000 (0.98-1.03)	0.978
549 EuroSCORE II ^o	0.095	1.100 (1.06-1.14)	0.001
550 Second vs. first case	0.717	2.048 (1.33-3.16)	0.001
551 Constant	- 2.816		

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554 Multivariable 30-days mortality analysis – surgeons operating both first and second case

555

556 Factor	Regression coefficient	Odds Ratio (95% CI)	P
558 Surgeon	0.010	1.010 (0.97-1.05)	0.611
559 EuroSCORE II ^o	0.112	1.118 (1.07-1.17)	0.001
560 Second vs. first case	0.615	1.850 (0.91-3.75)	0.088
561 Constant	- 4.236		

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° Corrected for 30-days mortality; CI: confidence interval

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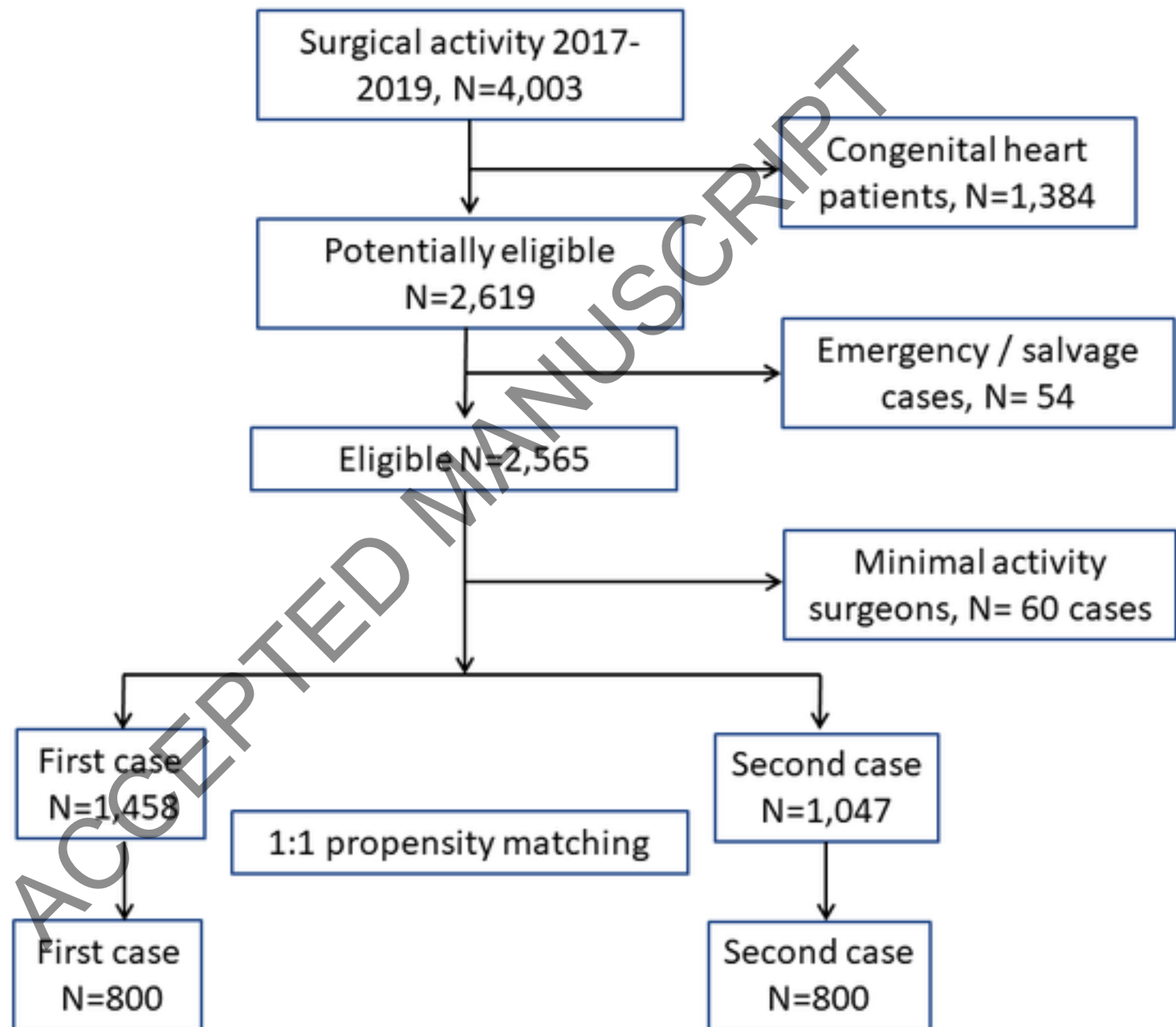
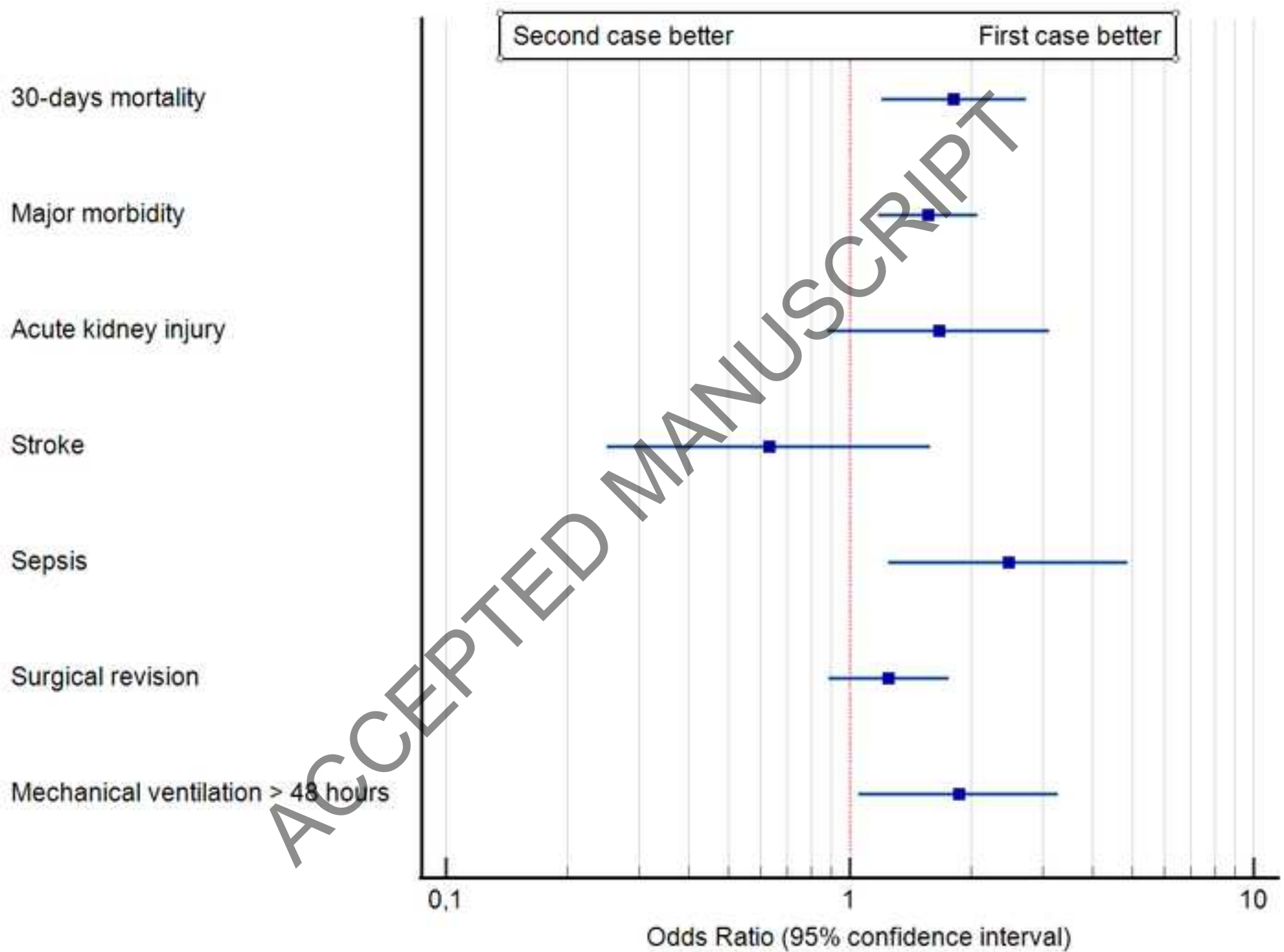
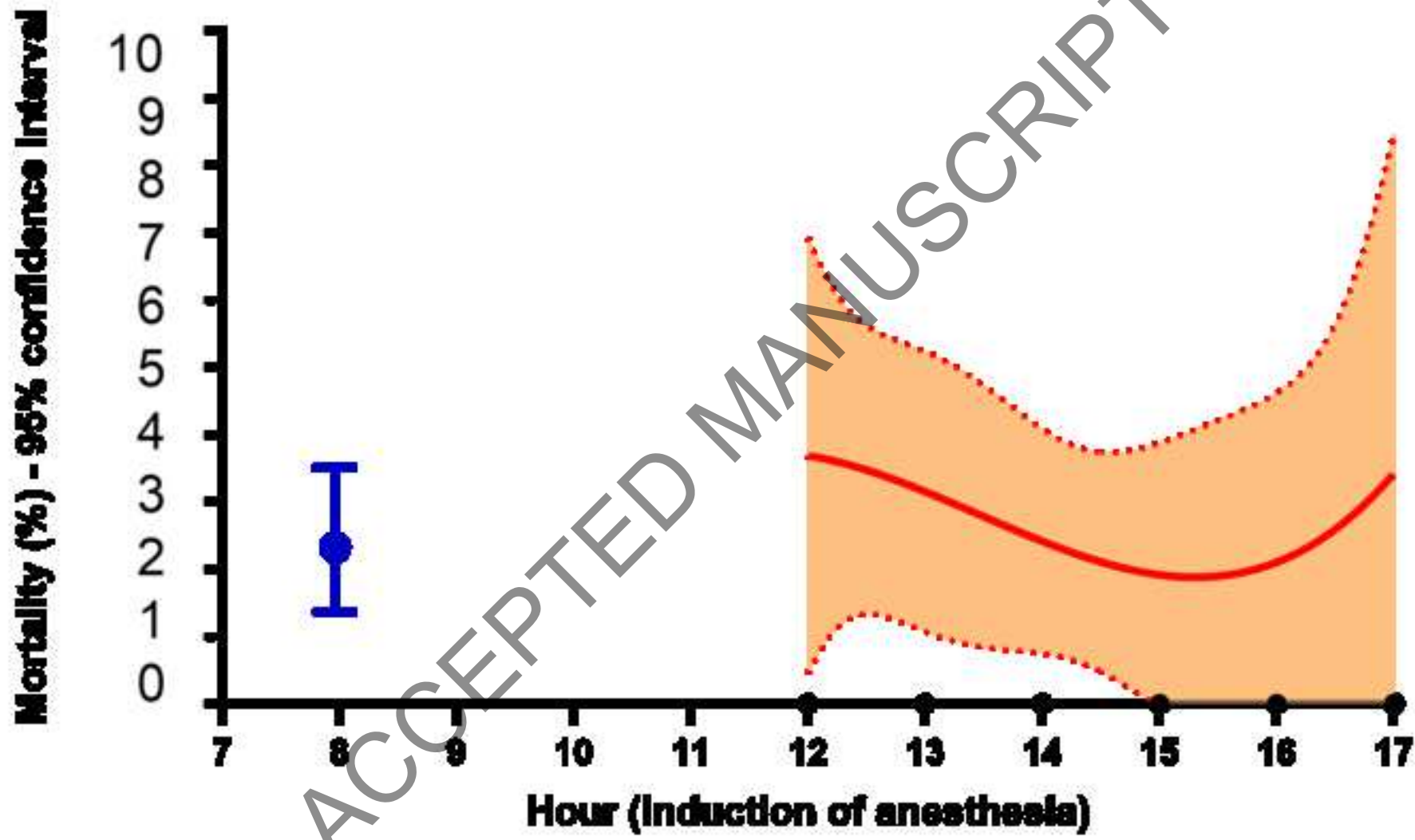
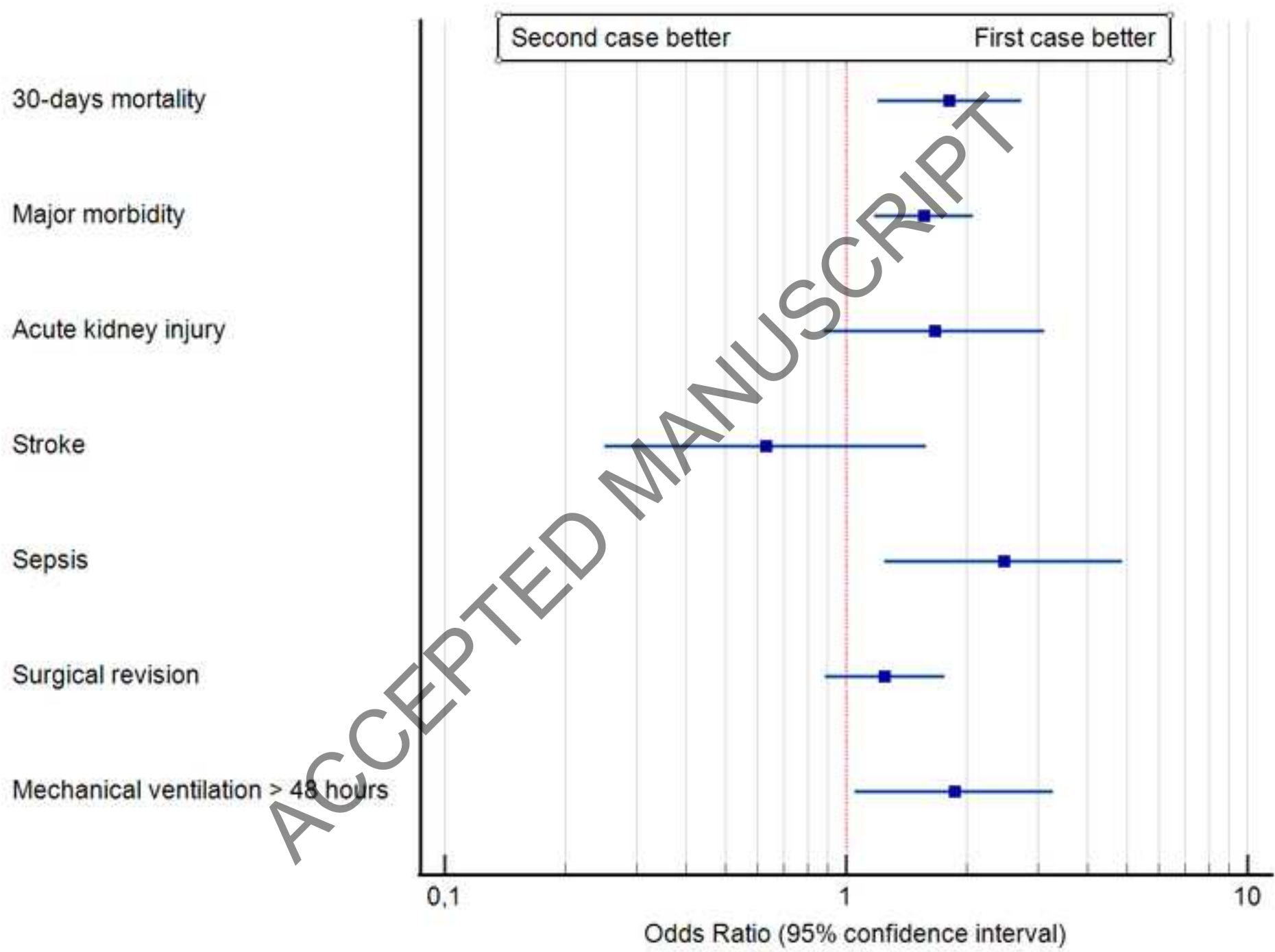


Figure 1





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