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Steroid administration after anaesthetic induction with etomidate does not reduce in-hospital mortality or cardiovascular morbidity after non-cardiac surgery

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Abstract

Background: We tested the primary hypothesis that corticosteroid administration after etomidate exposure reduces a composite of in-hospital mortality and cardiovascular morbidity after non-cardiac surgery.
Methods: We evaluated ASA physical status III and IV patients who had non-cardiac surgery with general anaesthesia at the Cleveland Clinic. Amongst 4275 patients in whom anaesthesia was induced with etomidate, 804 were also given steroid intraoperatively, mostly dexamethasone at a median dose of 6 mg. We successfully matched 582 steroid patients with 1023 non-steroid patients. The matched groups were compared on composite of in-hospital mortality and cardiovascular morbidity using a generalized-estimating-equation model. Secondly, the matched groups were compared on length of hospital stay using a Cox proportional hazard model, and were descriptively compared on intraoperative blood pressures using a standardized difference.
Results: There was no significant association between intraoperative steroid administration after anaesthetic induction with etomidate and the composite of in-hospital mortality or cardiovascular morbidity; the estimated common odds ratio across the two components of the composite was 0.86 [95% confidence interval (CI): 0.64, 1.16] for steroid *vs* non-steroid, $P=0.33$. The duration of postoperative hospitalisation was significantly shorter amongst steroid patients [median (Q1, Q3): 6 (3, 10) days] than non-steroid patients [7 (4, 11) days], with an estimated hazard ratio of 0.89 (0.80, 0.98) for steroid *vs* non-steroid, $P=0.01$. Intraoperative blood pressures were similar in steroid and non-steroid patients.
Conclusions: Steroid administration after induction of anaesthesia with etomidate did not reduce mortality or cardiovascular morbidity.

Keywords: adrenal cortex hormones; anaesthesia; etomidate

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Key points

- A single dose of etomidate causes adrenal suppression, which can last >24 h in the critically ill.
- Etomidate use for anaesthetic induction is associated with adverse outcomes in high-risk patients.
- Using a patient database, the authors assessed the influence on the outcome of steroid supplementation after etomidate in high-risk patients.
- Steroid administration did not reduce mortality or cardiovascular morbidity.

Etomidate, at typical anaesthetic induction doses, causes adrenal suppression[1] that lasts at least 6 h in healthy patients[2] and >24 h in those who are critically ill.[3,4] Etomidate thus seems likely to exacerbate the already substantial risk of adrenal insufficiency in high-risk surgical patients. Consistent with this theory, we recently reported that there is an association between etomidate and adverse outcomes in the ASA physical status III and IV adults having non-cardiac surgery. Specifically, patients given etomidate for anaesthetic induction had significantly greater odds of in-hospital postoperative mortality [odds ratio (OR), 2.5; 98% confidence interval (CI), 1.8–3.3] and significantly greater odds of having cardiovascular morbidity (OR, 1.5; 98% CI, 1.2–2.0).[5]

Adrenal suppression seems a likely explanation for worse outcomes in patients given etomidate. But, it remains unclear whether steroid administration after etomidate exposure blunts the putative harmful effects of etomidate. In sepsis[6] and septic shock,[7–9] most studies do not report a mortality benefit from steroid supplementation,[6–9] although one study showed shorter mechanical ventilation times and a lower requirement for vasopressors.[8] In predominantly trauma populations, a study showed decreased vasopressor requirement,[10] whilst the other showed decreased mechanical ventilation time, decreased incidence of hospital-acquired pneumonia, and shorter intensive-care-unit (ICU) stays.[11]

We thus tested the primary hypotheses that amongst ASA physical status III and IV adults having non-cardiac surgery under general anaesthesia induced with etomidate, intraoperative steroid administration reduces a composite of in-hospital mortality and major in-hospital cardiovascular morbidity.

Methods

With institutional review board approval and waived informed consent, we queried the Perioperative Health Documentation System Registry of the Cleveland Clinic between May 2005 and September 2015. The Cleveland Clinic's Perioperative Health Documentation System contains all patients who had non-cardiac surgery at the Cleveland Clinic Main Campus since May 2005. It integrates preoperative variables (patient and baseline characteristics), intraoperative variables from our anaesthesia record-keeping system (Talis Clinical, Inc., Streetsboro, Ohio, USA), and postoperative outcomes (by linking to Cleveland Clinic billing and other systems).

The study population consisted of ASA physical status III and IV adults having non-cardiac inpatient surgery, in which general anaesthesia was induced with etomidate, with or without a combined regional anaesthesia. Anaesthesia was maintained with a volatile anaesthetic, supplemented per clinical preference with opioids and neuromuscular blocking agents. Patients who used systemic steroids before operation were excluded.

We matched each patient who received intraoperative steroid (steroid patients) to a maximum of two patients who did not (non-steroid patients), using propensity-score matching[12] to control for observed potential confounding. First, we estimated the probability of receiving intraoperative steroid (i.e. propensity score) for each patient using logistic regression with steroid (*vs* non-steroid) as the outcome, and all prespecified patient and baseline characteristics as independent variables. Matching was then implemented using a greedy algorithm (SAS macro: gmatch, SAS Institue Inc., Cary, North Carolina, USA[13]), restricting successful matches to those with the same type of surgery and those whose estimated propensity-score logits [i.e. $\log\left(\frac{\hat{p}}{1-\hat{p}}\right)$, $\hat{p}$: estimated propensity score] were within 0.2 propensity-score logit standard deviations of each other.

Surgery type was characterized into one of the 244 mutually exclusive clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software for the International Classification of Diseases, Ninth Revision, Clinical Modification procedure codes. Single imputation using the monotone propensity-score method[14] based on all baseline characteristics and outcomes was implemented for BMI, which was missing for 7.7% of all patients.

Assessment of balance on the covariates used for the propensity-score matching was performed using absolute standardized differences (ASD, i.e. the absolute difference in means or proportions divided by the pooled standard deviation). Imbalance was defined as an ASD greater than 0.1; any such covariates were included in the models so as to reduce potential confounding when comparing steroid and non-steroid patients on outcomes. All of the analyses were based on this subset of matched patients.

Primary outcomes

The matched steroid and non-steroid patients were compared on the collapsed composite of in-hospital mortality and cardiovascular morbidity (Table 1). We assessed the 'common effect' of intraoperative steroid across the two individual components of the composite using a generalized-estimating-equation (GEE) model with an unstructured covariance matrix.[15] We reported the individual ORs from the distinct-effect GEE model regardless of the significance of the heterogeneity

Table 1 Description of postoperative cardiovascular morbidity. ICD-9-CM, Clinical Classifications Software for the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic code. NOS, not otherwise specified

ICD-9-CM	Description
458.29	Other iatrogenic hypotension; postoperative hypotension
997.1	Cardiac arrest, insufficiency, cardiorespiratory failure, and heart failure during or resulting from a procedure
998.0	Postoperative shock; collapse NOS and shock (endotoxic, hypovolaemic, and septic) during or resulting from a surgical procedure

along with the overall common-effect OR. A Bonferroni correction for multiple comparisons was used to control the Type I error at 0.05, so that $P<0.025$ was considered significant for each individual component (i.e. 0.05/2=0.025).

Secondary outcomes

Within the propensity-score-matched subset of steroid and non-steroid patients, we also assessed the association between intraoperative steroid administration and length of hospital stay. We built a Cox proportional hazard model[16] with 'discharged alive' as the outcome event. Patients who died in a hospital were considered as never having the event and were assigned a censoring time 1 day greater than the observed longest duration of the hospitalisation amongst those discharged alive.

Additionally, as adrenal insufficiency has been associated with hypotension, to see if corticosteroid supplementation after etomidate is associated with more stable intraoperative haemodynamics (i.e. less hypotension) in comparison to those who were not treated with corticosteroid, we showed the within-patient average and minimum of systolic and diastolic blood pressure in each intraoperative period (i.e. from induction to intubation, intubation to incision, incision to closing, closing to emergence, and emergence to end of case). Differences between the matched steroid and non-steroid patients were estimated using a standardized difference.

We used all patients who met the study inclusion/exclusion criteria. With 1605 matched patients, we had about 90% power at the 0.05 significance level to detect a common-effect OR of 0.6 or stronger across the two components of the composite of in-hospital mortality and cardiovascular morbidity for steroid patients *vs* non-steroid patients, assuming incidences of 5% for in-hospital mortality and 10% for cardiovascular morbidity, and assuming a compound symmetric correlation structure with a between-outcome correlation of 0.05. The power calculation was based on 1000 simulations using an SAS macro developed for designs with multiple binary correlated end points ('multibinpow').[17] The SAS program uses simulations to compute and display comparative power of several parallel-group multivariate tests for treatment effect on a vector of binary events.[18] SAS software, version 9.4 (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

We identified 4275 patients who met the inclusion and exclusion criteria, including 804 steroid patients (19%) and 3471 non-steroid patients (81%). Amongst the 804 steroid patients, 57% received dexamethasone, 26% received hydrocortisone, 16% received methylprednisolone, and 1% received other types. Based on patient and baseline characteristics, we successfully matched 582 steroid patients (72% of 804 steroid patients) with 1023 non-steroid patients. Specifically, the steroid and non-steroid patients were exactly matched on the type of surgery, and were much better balanced on other covariates as a result of propensity-score matching (Table 2; Fig. A1). Only the history of carotid disease and year of surgery were slightly imbalanced (ASD >0.1) after the propensity-score matching, which were adjusted in all analyses comparing steroid and non-steroid patients. The ASD was not reported for the type of surgery for two reasons. First, ASD is not meaningful for a categorical variables with 244 levels. Secondly, we matched the patients on the type of surgery exactly, and so no need to assess the balance after the matching.

Amongst the 1605 matched patients, the median dose of etomidate was 20 (Q1, Q3: 16, 20) mg given within 10 min of induction. Amongst the 582 matched steroid patients, 64% received dexamethasone at a median dose of 6 (Q1, Q3: 6, 8) mg, 32% received hydrocortisone [100 (100, 100) mg], and 4% received methylprednisolone [1000 (500, 1000) mg]. The median interval between the administration of etomidate and steroid was 34 (13, 68) min; specifically, the time interval was 35 (16, 64) min for dexamethasone, 25 (6, 61) min for hydrocortisone, and 259 (53, 281) min for methylprednisolone.

Primary outcomes

Within the matched subset of patients, no significant association was found between the intraoperative steroid administration and the composite of in-hospital mortality or cardiovascular morbidity; the estimated common effect across the two components of the composite was 0.86 (0.64, 1.16) for steroid *vs* non-steroid ($P=0.33$; Table 3). The incidence of in-hospital mortality was 4.6% for both steroid and non-steroid patients, with an estimated OR of 1.01 (97.5% CI: 0.58, 1.76) for steroid *vs* non-steroid; $P=0.97$. Likewise, the incidence of having postoperative cardiovascular morbidity was 9.8% for steroid patients and 12.1% for non-steroid patients, with an estimated OR of 0.79 (97.5% CI: 0.54, 1.15) for steroid *vs* non-steroid; $P=0.16$.

Secondary outcomes

Steroid administration after the anaesthetic induction with etomidate was significantly associated with shorter length of hospital stay (log-rank test; $P=0.01$; Fig. A2). The estimated median durations of postoperative hospitalisation from the Kaplan–Meier curve were 6 (Q1, Q3: 3, 10) days for steroid patients and 7 (4, 11) days for non-steroid patients. The estimated hazard ratio of staying in the hospital after surgery was 0.89 (95% CI: 0.80, 0.98) for steroid *vs* non-steroid, after adjusting for history of carotid disease and year of surgery ($P=0.01$). Discharges for patients who died in the hospital were considered as non-events and censored at the longest observed length of stay.

The within-patient average and minimum of systolic and diastolic blood pressure during any intraoperative period were similar in the steroid and non-steroid patients, and is summarized by standardized differences in Table 4.

Discussion

Intraoperative administration of steroids was not associated with decreased in-hospital mortality and cardiovascular morbidity in ASA physical status III and IV inpatients having non-cardiac surgery in which general anaesthesia was induced with etomidate (our primary outcome). The median length of hospital stay was shorter in patients given steroids (6 days) than for non-steroid patients (7 days; $P=0.01$), but this secondary outcome was probably of marginal clinical importance.

In a predominantly elective surgical population, a single dose of etomidate suppresses serum cortisol concentration for 6–24 h,[2,19] and the studies that used the cosyntropin stimulation test have shown that relative adrenal insufficiency caused by etomidate lasts up to 24 h.[20,21] Whether etomidate-induced

Table 2 Patient and baseline characteristics for patients with and without intraoperative steroid supplementation before and after propensity-score matching. Summary is reported as median [Q1, Q3] or 'N (%)', as appropriate. ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal; HIV, human immunodeficiency virus; HPA, hypothalamic–pituitary–adrenal. *ASD: the absolute difference in means or proportions divided by the pooled standard deviation; any covariables with ASD ≥0.10 after the propensity-score matching were adjusted for in the analyses. †The ASD was not reported for the type of surgery for two reasons. First, ASD is not meaningful for a categorical variable with 244 levels. Secondly, we matched the patients on the type of surgery exactly, and so there was no need to assess the balance after the matching. ‡7.7% of BMI values were imputed on the basis of all available baseline intraoperative and outcomes using propensity-score method. ¶Surgery type was classified based on 244 mutually exclusive clinically appropriate categories using the Agency for Healthcare Research and Quality's single-level Clinical Classifications Software for the International Classification of Diseases, Ninth Revision, Clinical Modification procedure codes. The 10 most frequent categories are reported because of the limited space

Variable	Before matching			After matching		
	Steroid (N=804)	Non-steroid (N=3471)	ASD*	Steroid (N=582)	Non-steroid (N=1023)	ASD*
Age, mean (minimum, maximum)	66 (19, 95)	71 (19, 100)	0.38	69 (19, 95)	69 (19, 99)	0.01
Female, N (%)	372 (46)	1360 (39)	0.14	264 (45)	456 (45)	0.02
Caucasian, N (%)	658 (82)	2819 (81)	0.02	485 (83)	828 (81)	0.06
BMI,‡ kg m^{-2}	27 [24, 32]	27 [24, 31]	0.07	27 [24, 32]	27 [24, 32]	0.00
ASA physical status, IV (*vs* III)	340 (42)	1490 (43)	0.01	226 (39)	398 (39)	0.00
Charlson co-morbidity score	3 [2, 5]	3 [2, 5]	0.04	3 [2, 5]	3 [2, 5]	0.01
Medical history, yes, N (%)						
Diabetes mellitus			0.06			0.05
Not diabetic	509 (63)	2190 (63)		382 (66)	658 (64)	
Non-insulin dependent	146 (18)	572 (16)		100 (17)	169 (17)	
Insulin dependent	149 (19)	709 (20)		100 (17)	196 (19)	
COPD	162 (20)	590 (17)	0.08	129 (22)	189 (18)	0.09
Dialysis	51 (6)	163 (5)	0.07	25 (4)	43 (4)	0.00
Angina pectoris	40 (5)	191 (6)	0.02	33 (6)	58 (6)	0.00
Myocardial infarction	104 (13)	528 (15)	0.07	85 (15)	130 (13)	0.06
Hypertension	586 (73)	2769 (80)	0.16	448 (77)	788 (77)	0.00
Congestive heart failure	260 (32)	1174 (34)	0.03	203 (35)	327 (32)	0.06
Valvular heart disease	203 (25)	887 (26)	0.01	153 (26)	261 (26)	0.02
Peripheral vascular disease	257 (32)	1612 (46)	0.30	215 (37)	344 (34)	0.07
Stroke	107 (13)	557 (16)	0.08	87 (15)	142 (14)	0.03
Carotid disease	125 (16)	599 (17)	0.05	107 (18)	151 (15)	0.10
HIV	1 (0)	2 (0)	0.02	0 (0)	1 (0)	0.04
Cancer	302 (38)	1176 (34)	0.08	216 (37)	389 (38)	0.02
HPA disorder	31 (4)	93 (3)	0.07	24 (4)	39 (4)	0.02
Year of surgery			0.30			0.18
2005	54 (7)	283 (8)		42 (7)	80 (8)	
2006	88 (11)	440 (13)		68 (12)	139 (14)	
2007	87 (11)	402 (12)		67 (12)	107 (10)	
2008	90 (11)	447 (13)		67 (12)	130 (13)	
2009	84 (10)	489 (14)		63 (11)	135 (13)	
2010	99 (12)	511 (15)		68 (12)	132 (13)	
2011	61 (8)	267 (8)		45 (8)	81 (8)	
2012	46 (6)	174 (5)		33 (6)	50 (5)	
2013	70 (9)	172 (5)		51 (9)	64 (6)	
2014	68 (8)	171 (5)		45 (8)	65 (6)	
2015	57 (7)	115 (3)		33 (6)	40 (4)	
Duration of surgery, h	4.3 [2.9, 6.6]	3.6 [2.6, 5.1]	0.33	3.7 [2.8, 5.3]	3.8 [2.8, 5.2]	0.02
Emergent case, yes, N (%)	128 (16)	684 (20)	0.10	89 (15)	174 (17)	0.05
Use of regional anaesthesia	68 (8)	496 (14)	0.18	63 (11)	116 (11)	0.02
Most frequent type of surgery¶			N/A†			N/A†
Other operative procedures on vessels other than head and neck	32 (10)	320 (21)		30 (13)	58 (13)	
Aortic resection, replacement, or anastomosis	25 (7)	308 (20)		25 (11)	50 (11)	
Colorectal resection	57 (17)	241 (16)		54 (23)	103 (24)	
Endarterectomy, vessel of head and neck	15 (4)	155 (10)		15 (6)	28 (6)	
Peripheral vascular bypass	14 (4)	123 (8)		14 (6)	28 (6)	
Hip replacement, total and partial	18 (5)	116 (8)		18 (8)	34 (8)	
Laminectomy, excision intervertebral disc	29 (9)	90 (6)		29 (12)	54 (12)	
Other operative gastrointestinal therapeutic procedures	21 (6)	97 (6)		16 (7)	27 (6)	
Other organ transplantation	98 (29)	13 (1)		13 (5)	13 (3)	
Other operative lower GI therapeutic procedures	27 (8)	83 (5)		23 (10)	43 (10)	

Table 3 Primary results: association between intraoperative supplementation of steroid and the composite of in-hospital mortality and cardiovascular morbidity using propensity-score-matched patients (n=1605). CI, confidence interval. 95% CI was estimated for the overall common effect across the two components of the composite outcome, and 97.5% CI was estimated for each individual component (Bonferroni correction, i.e. 0.05/2). †The definition of cardiovascular morbidity is reported in Table 1

Primary outcome	Incidence, N (%)		Odds ratio (95% CI) (steroid *vs* non-steroid)	P
	Steroid (N=582)	Non-steroid (N=1023)		
In-hospital mortality	27 (4.6)	47 (4.6)	1.01 (0.58, 1.76)	0.97
Cardiovascular morbidity†	57 (9.8)	124 (12.1)	0.79 (0.54, 1.15)	0.16
Common effect across the above two components			0.86 (0.64, 1.16)	0.33

adrenal suppression translates into adverse clinical outcomes is controversial. In cardiac surgical patients, Iribarren and colleagues[22] showed that the patients who received etomidate required a higher dose of vasopressors during the postoperative period than those who received other induction agents, whilst other studies found no difference in vasopressor requirement[20] and outcomes, including mechanical ventilation time and length of ICU and hospital stay, between etomidate and other induction agents.[21,23,24] In non-cardiac surgery, one study demonstrated no differences in intraoperative haemodynamic parameters, vasopressor requirement,[19] and length of hospital stay between etomidate and propofol, although our previous work showed an increased incidence of postoperative cardiovascular morbidities.[5]

Information regarding the effect of corticosteroid supplementation after etomidate exposure in an elective surgical population is scarce. By using a 3 day tapering hydrocortisone supplementation regimen, starting at 300 mg daily on the day of surgery followed by 200 mg daily on Day 1 and 100 mg daily on Day 2, Basciani and colleagues[21] showed no benefit of corticosteroid supplementation after etomidate exposure with regard to vasopressor requirement, mechanical ventilation time, length of ICU stay, and mortality. The patients in the current study were given a single relatively low intraoperative dose of dexamethasone, hydrocortisone, or methylprednisolone. It is thus likely that etomidate-induced adrenal suppression, which can exceed 24 h,[3] outlasted the steroid effect in our patients, and the putative benefit of corticosteroid supplementation might not manifest clinically in the current study.

In our previous study, also based on an analysis of the Cleveland Clinic perioperative registry,[5] we observed a marginally prolonged hospitalisation in patients given etomidate *vs* propofol for anaesthetic induction (median: 7 days *vs* 6 days). In the current analysis, which was restricted to patients given etomidate, the median length of hospital stay was 6 days in patients given steroid and 7 days in those who were not (P=0.01). Whilst it is tempting to attribute shortened hospitalisation in patients given steroids to 'reversal' of etomidate-induced adrenal suppression, we note that there may be beneficial effects of steroid unrelated to adrenal function, including reduced postoperative pain[25] and fatigue.[26]

Steroid administration was not randomly assigned; instead, it was provided at the discretion of attending anaesthesiologists. To reduce selection bias attributable to observed covariates, we matched the patients exactly on type of surgery, and then used propensity-score matching to develop comparable comparison groups. The groups were in fact well balanced on observed factors potentially influencing outcomes of interest. But, there possibly remains a degree of selection bias and confounding related to factors that were unavailable in our electronic records, and yet-to-be-identified confounding factors.

For example, we were unable to adjust for the fact that various surgical approaches are characterized by the same surgical billing codes. Because data were not available electronically, we were also unable to account for a number of factors that potentially affect adrenal function, such as postoperative steroid use, and preoperative use of medications that inhibit cortisol biosynthesis (i.e. ketoconazole, metyrapone, and suramin) or those that increase steroid metabolism (i.e. carbamazepine, phenobarbital, phenytoin, rifampicin, and mitotane). Further, although we showed similar intraoperative haemodynamic parameters between those who received and did not receive steroid, as the information regarding intraoperative vasopressors and inotrope doses was not available, we cannot conclude that both groups had similar haemodynamic stability. As with all observational studies, we report statistical associations, which may or may not indicate causal relationships between steroid

Table 4 Summary of intraoperative blood pressure for propensity-score-matched patients (n=1605). ASD, absolute standardized difference; SBP, systolic blood pressure; DBP, diastolic blood pressure. *ASD: the absolute difference in means or proportions divided by the pooled standard deviation

Blood pressure	Steroid (N=582)	Non-steroid (N=1023)	ASD*
Induction to intubation	N=500	N=869	
Mean SBP	146 (31)	146 (33)	0.00
Mean DBP	70 (15)	70 (16)	0.00
Minimum SBP	138 (32)	138 (33)	0.00
Minimum DBP	66 (15)	66 (16)	0.00
Intubation to incision	N=580	N=1020	
Mean SBP	128 (22)	126 (22)	0.09
Mean DBP	63 (12)	62 (12)	0.08
Minimum SBP	96 (21)	94 (22)	0.11
Minimum DBP	47 (12)	46 (12)	0.10
Incision to closing	N=582	N=1022	
Mean SBP	125 (17)	123 (16)	0.12
Mean DBP	62 (10)	62 (11)	0.04
Minimum SBP	92 (18)	90 (17)	0.16
Minimum DBP	46 (11)	45 (10)	0.09
Closing to emergence	N=569	N=1006	
Mean SBP	123 (19)	123 (19)	0.03
Mean DBP	61 (12)	60 (11)	0.01
Minimum SBP	108 (20)	106 (20)	0.11
Minimum DBP	53 (11)	52 (12)	0.07
Emergence to end of case	N=576	N=992	
Mean SBP	138 (24)	138 (25)	0.00
Mean DBP	66 (13)	66 (14)	0.04
Minimum SBP	116 (25)	116 (26)	0.03
Minimum DBP	53 (15)	54 (16)	0.05

administration after etomidate use and adverse outcomes. And finally, this was a single-centre study; results may differ in other settings and in other populations.

In summary, in our analysis of ASA physical status III and IV non-cardiac surgical inpatients that were given etomidate for induction of general anaesthesia, intraoperative steroid administration (mostly at doses suitable for nausea and vomiting prophylaxis) was not associated with decreased odds of in-hospital mortality or cardiovascular morbidity. Steroid administration was associated with a slightly shorter duration of hospitalisation, a finding that is probably of only marginal clinical importance.

Authors' contributions

Study design, data analysis and interpretation, drafting and final approval of the manuscript: all authors.
Data collection: J.Y.

Declaration of interest

None of the authors have any financial interests to disclose.

Appendix.

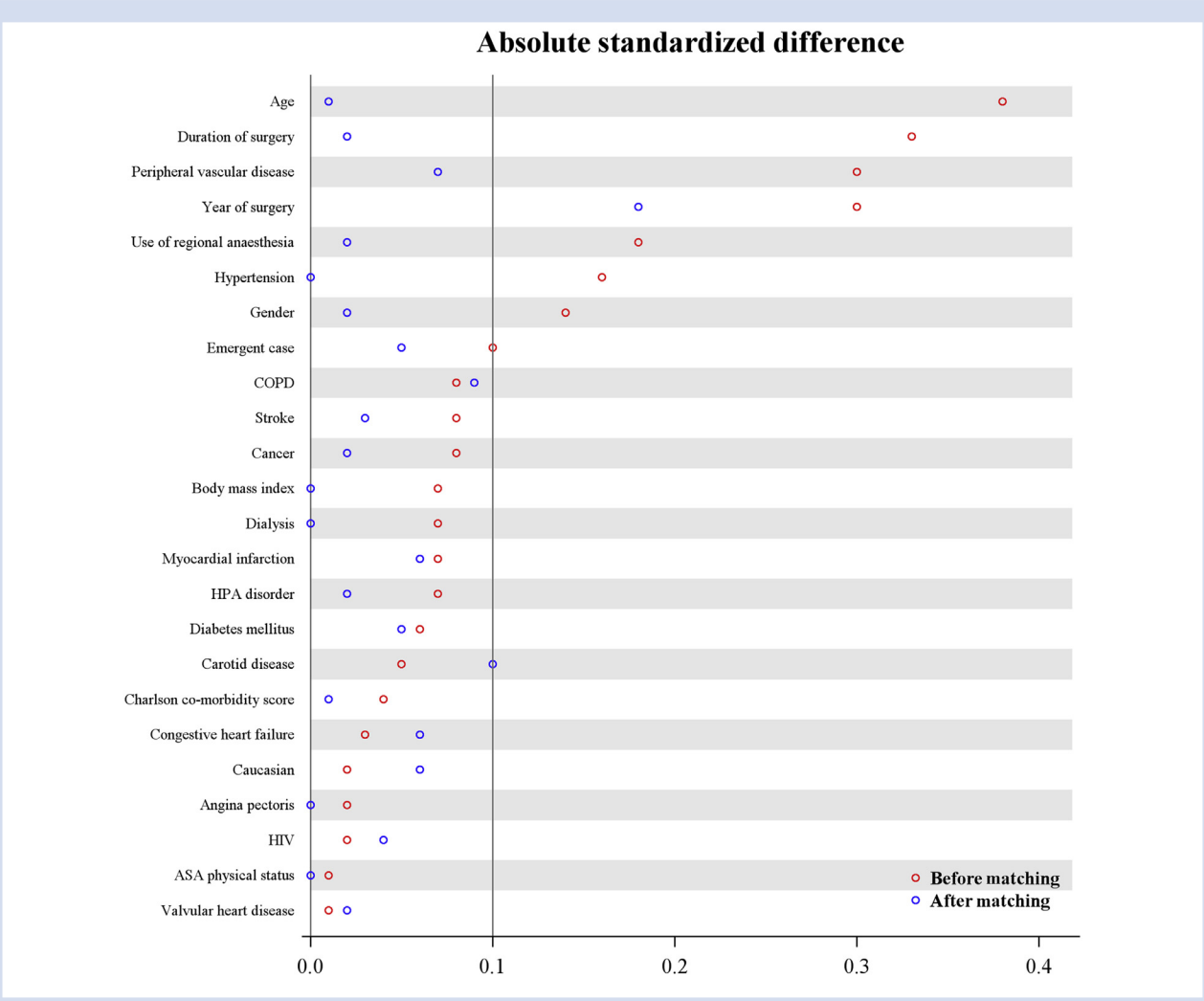

Fig. A1. Plot of absolute standardized difference of co-variables used to estimate the propensity score before and after the propensity-score matching. COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HPA, hypothalamic–pituitary–adrenal.

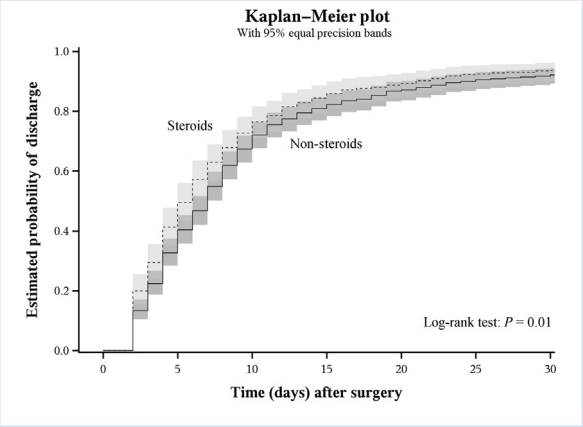

Fig. A2. Kaplan–Meier estimates of probability of being discharged from hospital (lines) and associated 95% equal-precision confidence bands (shaded regions) for propensity-score-matched steroid (N=582) and non-steroid patients (N=1023). Patients who died in the hospital were considered as not being discharged and censored at the longest observed length of stay; thus, the curves did not reach 100% at the end. These univariable Kaplan–Meier estimates were statistically different between steroid and non-steroid patients (log-rank test; P=0.01).

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