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Original Article

Rapid uptake of adjunctive corticosteroids for critically ill adults with septic shock following publication of ADRENAL trial. A multicenter, retrospective analysis of prescribing practices in Queensland Intensive Care Units

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ABSTRACT

Background: Septic shock is common and associated with significant morbidity and mortality. The ADRENAL trial examined the use of hydrocortisone in patients with septic shock, demonstrating no difference in patient-centred outcomes but a decrease in the time to shock resolution. The change in clinical practice related to the publication of the ADRENAL trial is currently unknown.
Methods: A retrospective cohort study examining the use of hydrocortisone in patients with septic shock was conducted in 12 intensive care units (ICUs). A segmented linear regression was performed to identify a stepwise change in hydrocortisone administration and 90-day mortality associated with the publication of the ADRENAL trial.
Results: We included 4,198 patients with a mean age of 58 years (standard deviation, SD17), and the median noradrenaline equivalent score (NEE) was 0.07 μg/kg/min (IQR 0.02–0.17). Segmented regression analysis for hydrocortisone administration identified two breakpoints, 3 months before and 6 months after publication, leading to three periods: Pre-publication, Transition, and Post-publication. Compared to the pre-publication period, the Transition and Post-publication cohorts had a higher proportion of hydrocortisone administration (28% *vs.* 34% *vs.* 43%; $p < 0.0001$). Furthermore, after adjustment for temporal change, the transition period had a significant change in the slope of the

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proportion of patients receiving hydrocortisone (−0.1% per month *vs.* +1.4% per month; $p = 0.026$), whereas this was not statistically significant during the post-publication period (+0.1% per month, p = 0.66). After adjusting for confounders, the Transition and Post-publication periods were independently associated with an increase in hydrocortisone (OR 1.4, 95% CI 1.14–1.77; $p = 0.0015$ and OR 2.03; 95% CI 1.74–2.36; $p < 0.001$, respectively). Furthermore, after adjusting for confounders, when compared to the Pre-transition period, the use of hydrocortisone was associated with a statistically significant decrease in 90-day mortality (14% *vs.* 24% absolute difference, aHR for hydrocortisone effect −0.81; 95% CI 0.65–0.99; $p = 0.044$).

Conclusion: Publication of the ADRENAL trial changed clinical practice in Queensland ICUs with increased prescription of hydrocortisone for patients with septic shock with an associated reduction in mortality.

Key Points

- Analysed the change in hydrocortisone administration in nearly 5,000 patients with septic shock in relation to the publication of the ADRENAL trial.
- The proportion of patients with septic shock receiving IV hydrocortisone increased over time.
- Despite the increase over time, as of the study's end date, less than half of patients with septic shock received IV hydrocortisone.
- After adjusting for the severity of illness, hydrocortisone use significantly reduced ICU length of stay and 90-day mortality.

Introduction

Sepsis and septic shock are critical conditions that continue to pose significant challenges in intensive care units (ICUs) worldwide [1,2]. These life-threatening syndromes are believed to result from an inappropriate host response to infection, leading to organ dysfunction [1,2]. Morbidity and mortality associated with sepsis and septic shock are profound, impacting both patients and healthcare systems [3,4]. Moreover, the incidence of septic shock is increasing in Europe [5].

The ADRENAL trial, a pivotal study in the field of sepsis management, investigated the use of steroids in patients with septic shock [6]. This multicenter, randomised, controlled trial evaluated the impact of hydrocortisone therapy on mortality and other clinical outcomes. The trial results revealed that early administration of low-dose hydrocortisone did not significantly reduce mortality rates in septic shock patients. However, it demonstrated a decrease in the duration of shock, suggesting steroid therapy may be a key component of a multimodal treatment strategy in septic shock [7].

Implementing clinical trials into practice is pivotal in bridging the gap between research findings and improved patient care [8,9]. Clinical trials generate valuable evidence regarding treatment efficacy, safety, and outcomes. However, this knowledge remains dormant unless effectively integrated into real-world clinical settings [8,10,11]. In critical care, where timely decisions impact patient survival, the absence of dedicated implementation work poses a significant challenge. Despite robust trial results, such as the ADRENAL trial, their translation into clinical practice remains an unmet need.

The primary objective of our research was to investigate the utilisation patterns of steroids in patients with septic shock in relation to the dissemination and publication of the ADRENAL trial results. We hypothesised that the ADRENAL trial publication may have influenced clinicians' decision-making processes, resulting in a rise in the prescription of steroids for septic shock treatment.

Methods

Study design and sites

We conducted a multicentre, retrospective cohort study of routinely collected electronic medical record (EMR)-based clinical data. The study evaluated patients between January 1st, 2015, and December 31st, 2021, from 12 closed-model, mixed (medical and surgical) ICUs in Queensland, Australia. The included ICUs were composed of 5 tertiary, 3 outer metropolitan, and 4 regional ICUs.

Data sources

Data was collected from all centres using eCritical MetaVisionTM (iMDsoft, Boston, MA, USA) clinical information systems [12–15] and the ANZICS CORE Adult Patient Database (APD) [16–19]. The data included daily laboratory reports, medications, microbiology, haemodynamics, fluid balance, patient demographics, diagnoses, severity of illness, and outcomes. Primary and secondary diagnoses, from the International Classification of Diseases 10 Australia Modification (ICD-10-AM) codes, as well as mortality data, were collected from the Queensland Hospital Admitted Patient Data Collection (QHAPDC) [20–22] and Queensland Births, Deaths, and Marriage Registry [23,24], respectively. As previously published, the amount of missing data for key variables in the dataset was very low [12]. Admission diagnoses were categorised to optimise data accuracy and interpretability (Supplementary Methods, Table S1). The Charlson-defined comorbidities and index were calculated from the ICD-10 codes (Supplementary Methods, Table S2) [25,26]. The noradrenaline formulation, noradrenaline bitartrate, was used at all sites during the study period [27]. The conversion of vasopressor dosage to noradrenaline equivalent and calculation of vasoactive inotrope score was carried out as per protocol (Supplementary Methods, Table S3 and S4) [28].

Patient inclusion and exclusion

All patients with retrievable and linked electronic medical records were evaluated for the inclusion and exclusion criteria. Most study sites recruited participants for the ADRENAL trial. Therefore, a sensitivity analysis was conducted, excluding patients admitted during recruitment dates for each study site.

Patients were included if their age was equal to or greater than 18 years of age at the time of ICU admission, had a diagnosis of septic shock, and were mechanically ventilated. Sepsis and septic shock were defined as per the SEPSIS-3 criteria [1]. Sepsis was electronically defined as an increase in SOFA score by two points and the administration, or escalation, of antimicrobial therapy along with microbiological sampling. Septic shock was determined

in patients with sepsis who required vasopressor therapy and had a lactate measurement >2 mmol/L. The method for electronic identification of sepsis and septic shock is based on previously published methods [12,29].

As per ADRENAL trial exclusion criteria, patients were excluded if admitted for palliative care or received amphotericin during their admission. In addition, patients transferred from another ICU, regardless of sepsis diagnosis, were excluded.

Identification of steroid administration

Medication administration was assessed for every day of ICU admission. Patients were considered to have received hydrocortisone for septic shock if administered within one day of septic shock diagnosis. In addition, fludrocortisone and other steroid administration were assessed using the same criteria.

The use of other steroids was also determined from the medications administered. All enteral and parenteral steroids, other than hydrocortisone and fludrocortisone, were assessed. This included: intravenous (IV) methylprednisolone, IV dexamethasone, enteral (PO) cortisone, PO hydrocortisone, and PO prednisolone.

Outcomes

The primary outcome of the study was the proportion of patients with septic shock who received hydrocortisone, in relation to the publication of the ADRENAL trial. The secondary outcome was all-cause 90-day mortality. Additional secondary outcomes days alive without vasopressors at day 30, days alive without invasive mechanical ventilation at day 30, length of stay in ICU and hospital, and mortality. A control outcome was the proportion of patients with septic shock who received continuous renal replacement therapy (CRRT) concerning the publication of the ADRENAL trial.

Statistical analysis

Descriptive statistics were expressed as frequencies and proportions for categorical variables and means with standard deviations or medians with interquartile ranges (IQR) depending on their parametric or non-parametric distribution, respectively. Pearson's Chi-squared test or Fisher's exact test was used to compare categorical variables. The Wilcoxon rank sum test was used to compare skewed continuous variables.

For each outcome of interest, a Davies test was performed to assess for a non-zero difference in slope over time. If significant, a segmented linear regression model, with data aggregated at a monthly level, was developed to examine outcome change over time. Segmented regression was used to evaluate whether there was a stepwise change in the value of each outcome of interest associated with the publication of the ADRENAL trial and whether there was a difference in the slope or rate of change over time. The associations between outcomes over time and two prespecified subgroups were performed. These subgroups were the ICU type, tertiary, outer metropolitan, and regional, and vasopressors dose, above or below the median noradrenaline equivalent dose (NEE) at the time of diagnosis of septic shock. To determine if hydrocortisone administration differed between the subgroups, the proportion of patients receiving hydrocortisone was analyzed using hierarchical mixed modelling with fitting of main effects for the period and subgroup and interaction between the two. Furthermore, a multivariable logistic regression was performed to determine which variables were associated with the primary outcomes. Variables were chosen *a priori* for the model based on available data and clinical significance as adjudicated by the investigators.

For secondary outcomes, the groups were categorized by a modified Pre-publication period, which includes Pre-publication and Transition periods, and unmodified Post-publication status, to facilitate comparison between groups. A multivariable Cox proportional hazards model was fitted to assess risk factors associated with 90-day mortality. Multivariable logistic and quantile regression models were used to assess risk factors associated with categorical and the median of continuous outcomes, respectively. Variables included were selected based on the full pre-specification method. According to the model, data are reported as hazard ratio (HR), odds ratio (OR), or β estimate together with a 95% confidence interval (95% CI). A two-sided *p*-value of <0.05 was chosen to indicate statistical significance. Statistical analyses were performed using R v.4.0.3.

Ethical considerations

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024) with an individual waiver of consent granted.

Results

Patient inclusion

From January 1st, 2015, and December 31st, 2021, there were 7,767 adult admissions to one of the 12 participating centres with septic shock. Of these, 145 were excluded for receiving amphotericin during their admission, and 2,269 were excluded for not requiring invasive mechanical ventilation, leaving 4,198 for inclusion in the main analysis. Of these, 3,178 patients were admitted outside of ADRENAL recruitment dates and analysed in a sensitivity analysis.

Patient characteristics

For the entire cohort, the mean age was 58 years (SD 17), and the mean Charlson co-morbidity index was 4 (SD 3). The most common co-morbidity was congestive heart failure (750; 18%), chronic pulmonary disease (571; 14%) and chronic kidney disease (556; 13%). According to APACHE diagnosis categorisation, only one in five patients were classified as having sepsis. Most patients were emergency admissions, admitted from the emergency department (1,720; 41%) or operating theatre (1,237; 29%). On admission to the ICU, the mean SOFA score was 9 (SD 3), and almost all patients required invasive mechanical ventilation (3,970; 95%). On the day of sepsis diagnosis, the median NEE score was 0.07 μg/kg/min (IQR 0.02 – 0.17), and the mean maximum lactate was 5.0 mmol/L (SD 4). The patient characteristics are summarised in Table 1.

Steroid administration

Over time, the segmented regression analysis assessed steroid administration, identifying two breakpoints: 3 months before and 6 months after publication. These breakpoints lead to three periods: Pre-publication, Transition and Post-publication (Fig. 1). A significant change in slope marked the transition period compared to the pre-publication period (from −0.1% per month to +1.4% per month in the transition period, $p = 0.026$). The post-publication also had a greater slope compared to the pre-publication period; however, this was not statistically significant (+0.1% per month, $p = 0.66$). The administration of steroids in the cohort is summarised in Supplementary Methods Table S5. There was no difference in the proportion of patients receiving CRRT over time (Supplementary Methods Figure S1).

Table 1
Baseline characteristics according to the time period.

Characteristic	N	Overall N = 4 198	Pre-publication N = 1 657	Transition N = 578	Post-publication N = 1 963
Demographic					
Age (years)	4 198	58 ± 17	59 ± 17	57 ± 17	58 ± 17
Female	4 198	1 742/4 198 (41)	709/1 657 (43)	237/578 (41)	796/1 963 (41)
Body Mass Index (kg/m2)	4 198	28 (24–32)	28 (25–31)	28 (24–33)	28 (24–33)
Comorbidities					
Charlson Co-morbidity Index	4 198	4 ± 3	4 ± 3	4 ± 3	4 ± 3
Ischaemic Heart Disease	4 198	411/4 198 (10)	162/1 657 (10)	61/578 (11)	188/1 963 (10)
Congestive Heart Failure	4 198	750/4 198 (18)	326/1 657 (20)	92/578 (16)	332/1 963 (17)
Peripheral Vascular Disease	4 198	250/4 198 (6)	105/1 657 (6)	36/578 (6)	109/1 963 (6)
Cerebrovascular Disease	4 198	372/4 198 (9)	166/1 657 (10)	54/578 (9)	152/1 963 (8)
Chronic Pulmonary Disease	4 198	571/4 198 (14)	230/1 657 (14)	79/578 (14)	262/1 963 (13)
Chronic Kidney Disease	4 198	556/4 198 (13)	227/1 657 (14)	77/578 (13)	252/1 963 (13)
Mild Liver Disease	4 198	212/4 198 (5)	90/1 657 (5)	32/578 (6)	90/1 963 (5)
Moderate-Severe Liver Disease	4 198	197/4 198 (5)	100/1 657 (6)	19/578 (3)	78/1 963 (4)
Diabetes	4 198	472/4 198 (11)	180/1 657 (11)	55/578 (10)	237/1 963 (12)
Diabetes with Complications	4 198	860/4 198 (20)	356/1 657 (21)	124/578 (21)	380/1 963 (19)
Localised Cancer	4 198	428/4 198 (10)	176/1 657 (11)	67/578 (12)	185/1 963 (9)
Metastatic Cancer	4 198	158/4 198 (4)	64/1 657 (4)	23/578 (4)	71/1 963 (4)
Admission					
ICU Level	4 198				
Tertiary		2 683/4 198 (64)	1 203/1 657 (73)	367/578 (63)	1 113/1 963 (57)
Outer Metropolitan		660/4 198 (16)	219/1 657 (13)	109/578 (19)	332/1 963 (17)
Regional		855/4 198 (20)	235/1 657 (14)	102/578 (18)	518/1 963 (26)
Source of Hospital Admission	4 198				
Home		3 082/4 198 (73)	1 182/1 657 (71)	436/578 (75)	1 464/1 963 (75)
Other Hospital		1 087/4 198 (26)	457/1 657 (28)	141/578 (24)	489/1 963 (25)
Low Acuity Facility		4/4 198 (0)	0/1 657 (0)	0/578 (0)	4/1 963 (0)
High Care Facility		25/4 198 (1)	18/1 657 (1)	1/578 (0)	6/1 963 (0)
Source of ICU Admission	4 198				
Emergency department		1 720/4 198 (41)	618/1 657 (37)	256/578 (44)	846/1 963 (43)
Operating Theatre		1 237/4 198 (29)	520/1 657 (31)	157/578 (27)	560/1 963 (29)
Ward		963/4 198 (23)	409/1 657 (25)	132/578 (23)	422/1 963 (21)
Other hospital		278/4 198 (7)	110/1 657 (7)	33/578 (6)	135/1 963 (7)
LOS in Hospital before ICU (hours)	4 196	8 (3–37)	8 (3–46)	8 (3–33)	8 (3–33)
APACHE Diagnosis Group	4 198				
Cardiovascular		699/4 198 (17)	263/1 657 (16)	105/578 (18)	331/1 963 (17)
Gastrointestinal		699/4 198 (17)	297/1 657 (18)	88/578 (15)	314/1 963 (16)
Genitourinary		170/4 198 (4)	69/1 657 (4)	24/578 (4)	77/1 963 (4)
Haematological		28/4 198 (1)	13/1 657 (1)	6/578 (1)	9/1 963 (0)
Metabolic		463/4 198 (11)	139/1 657 (8)	62/578 (11)	262/1 963 (13)
Neurological		485/4 198 (12)	187/1 657 (11)	70/578 (12)	228/1 963 (12)
Other		129/4 198 (3)	60/1 657 (4)	19/578 (3)	50/1 963 (3)
Respiratory		591/4 198 (14)	235/1 657 (14)	73/578 (13)	283/1 963 (14)
Sepsis		879/4 198 (21)	365/1 657 (22)	121/578 (21)	393/1 963 (20)
Trauma		55/4 198 (1)	29/1 657 (2)	10/578 (2)	16/1 963 (1)
Treatment Goals on Admission	4 198				
Full active treatment		3 842/4 198 (92)	1 531/1 657 (92)	524/578 (91)	1 787/1 963 (91)
Treatment limitation order		356/4 198 (8)	126/1 657 (8)	54/578 (9)	176/1 963 (9)
Prognostic scores					
APACHE 2 Score	4 197	21 ± 9	22 ± 9	21 ± 8	21 ± 8
APACHE 3 Score	4 197	70 ± 30	75 ± 32	67 ± 29	67 ± 28
APACHE 3 Risk of Death	4 197	27 ± 27	31 ± 28	26 ± 26	24 ± 25
Maximum SOFA score	4 198	9 ± 3	9 ± 3	9 ± 3	8 ± 3
Day of sepsis diagnosis					
Invasive mechanical ventilation	4 198	3 970/4 198 (95)	1 572/1 657 (95)	545/578 (94)	1 853/1 963 (94)
Minimum PF Ratio	3 791	196 ± 99	197 ± 101	192 ± 97	195 ± 97
Vasopressors	4 198	4 035/4 198 (96)	1 596/1 657 (96)	556/578 (96)	1 883/1 963 (96)
NEE Score (μg/kg/min)	4 198	0.07 (0.02–0.17)	0.07 (0.02–0.17)	0.06 (0.01–0.17)	0.07 (0.02–0.18)
Mean arterial blood pressure (mmHg)	4 189	75 ± 8	74 ± 8	75 ± 9	75 ± 8
Maximum Creatinine (μmol/L)	3 584	164 ± 144	167 ± 146	167 ± 178	161 ± 131
Renal Replacement Therapy	3 170	603/3 170 (19)	236/1 254 (19)	76/424 (18)	291/1 492 (20)
Maximum Lactate (mmol/L)	4 186	5 ± 4	5 ± 4	5 ± 4	5 ± 4
Maximum Bilirubin (μmol/L)	3 554	33 ± 49	32 ± 47	35 ± 62	32 ± 45
Maximum White Cell Count ($\times 10^9$/L)	3 518	17 ± 13	16 ± 13	17 ± 14	17 ± 13

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; LOS, Lenght of stay; ICU, intensive care unit; NEE, Noradrenaline equivalence; SOFA, Sequential Organ Failure Assessment.
Continous variables are presented as mean ± SD or median (Q1-Q3). Categorical variables are presented as n/N (%).

Compared to the Pre-publication and Transition cohorts, the Post-publication cohort had a higher proportion of hydrocortisone administration (28% *vs.* 34% *vs.* 43%; $p < 0.0001$). In patients who received hydrocortisone, both the duration of hydrocortisone (4 days [IQR 2–6] *vs.* 3 days [IQR 2–5] *vs.* 3 days [IQR 2–5]; $p = 0.82$) and the mean daily dose of hydrocortisone (175 mg/day [IQR 121–242] *vs.* 164 mg/day [IQR 125–243] *vs.* 162 mg/day [128–208]; $p = 0.45$) were similar in comparing Pre-publication, Transition, and Post-publication cohorts (Supplementary Methods Table S5). The administration of fludrocortisone was uncommon, with no

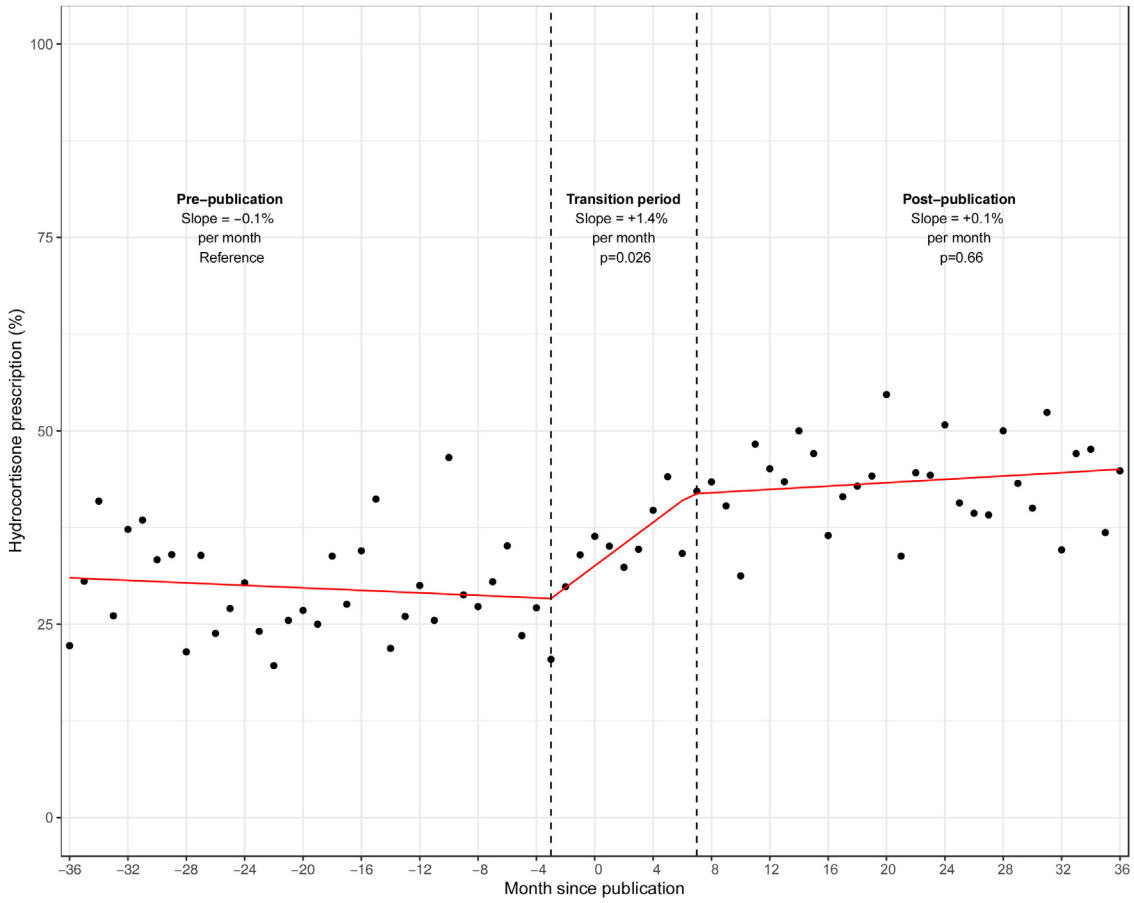

Fig. 1. Proportion of Patients receiving Hydrocortisone over time.
Points represent the estimated proportion of hydrocortisone prescriptions with a 95% confidence interval in light-shaded areas. The red line represents the segmented linear regression of hydrocortisone prescription over time with a 95% confidence interval of the fitted model in dark grey. *P*-value is calculated for the change in slope with respect to the Pre-publication period.

difference over time (0.4% *vs.* 0.9% *vs.* 0.4%; $p = 0.33$). The administration of parenteral or enteral steroids other than hydrocortisone or fludrocortisone was uncommon, and when compared to all three time periods with significantly more administered during the Transition time (6.8% *vs.* 9.9% *vs.* 6.5%; $p = 0.017$).

The proportion of patients receiving hydrocortisone over time was examined, and the patients were differentiated by NEE score on the day of septic shock diagnosis above or below 0.07 mcg/kg/min (Fig. 2). Patients receiving lower NEE doses were less likely to receive hydrocortisone throughout the time examined (OR 0.26; 95% 0.23 – 0.30; $p < 0.001$). However, there was no difference in change in the administration of hydrocortisone over time between low and high-dose NEE doses.

The administration of hydrocortisone over time was examined by type of ICU. Throughout all periods, compared to Tertiary ICUs, Regional ICUs (OR 1.44; 95% CI 1.23–1.68; $p < 0.001$) and Outer Metropolitan ICUs (OR 1.41; 95%CI 1.18–1.67; $p = 0.001$) were both more likely to administer hydrocortisone for septic shock. In contrast, compared to the Pre-Publication cohort, the proportion of patients receiving hydrocortisone in the Transition and Post-Publication cohorts increased in Tertiary ICUs. Still, it demonstrated no change over time in Outer Metropolitan and Regional ICUs (Fig. 3).

The multivariable logistic regression determined that both the transition and post-publication periods were independently associated with an increase in hydrocortisone prescription (OR 1.4, 95% CI 1.14–1.77; $p = 0.0015$ and OR 2.03; 95% CI 1.74–2.36; $p < 0.001$, respectively). In addition, AKI stage, NEE score, type of site, peak lactate, immunosuppression, and APACHE 3 score were independently associated with increased hydrocortisone administration (Table 2). Survival curves over 90 days are demonstrated in Fig. 4.

Lastly, a sensitivity analysis, excluding ADRENAL recruitment dates from sites that participated in the ADRENAL trial, did not demonstrate any difference to the cohort or the primary outcome (Supplementary Methods Table S9 and Figure S2).

Clinical outcomes

The clinical outcomes for the cohort are displayed in Table 3. After adjusting for severity of illness, age, lactate, site type, and comorbidities, when compared to the Pre-transition period, the use of hydrocortisone was associated with a statistically significant decrease in 90-day mortality (14% *vs.* 24% absolute difference, aHR for hydrocortisone effect −0.81; 95% CI 0.65–0.99; $p = 0.044$). There was no difference in hospital or ICU mortality or days alive without invasive mechanical ventilation or vasopressors (Table 3).

The detailed multivariable Cox model for 90-day mortality that demonstrated hydrocortisone was independently associated with a risk reduction is presented in Supplementary Methods Table S6. In addition to hydrocortisone, peak lactate, age, regional ICU, chronic respiratory disease, chronic liver disease, chronic hemopathy or cancer, and APACHE III score were also independently associated with an increased risk of 90-day mortality. Furthermore, after adjustment for confounders, hydrocortisone was

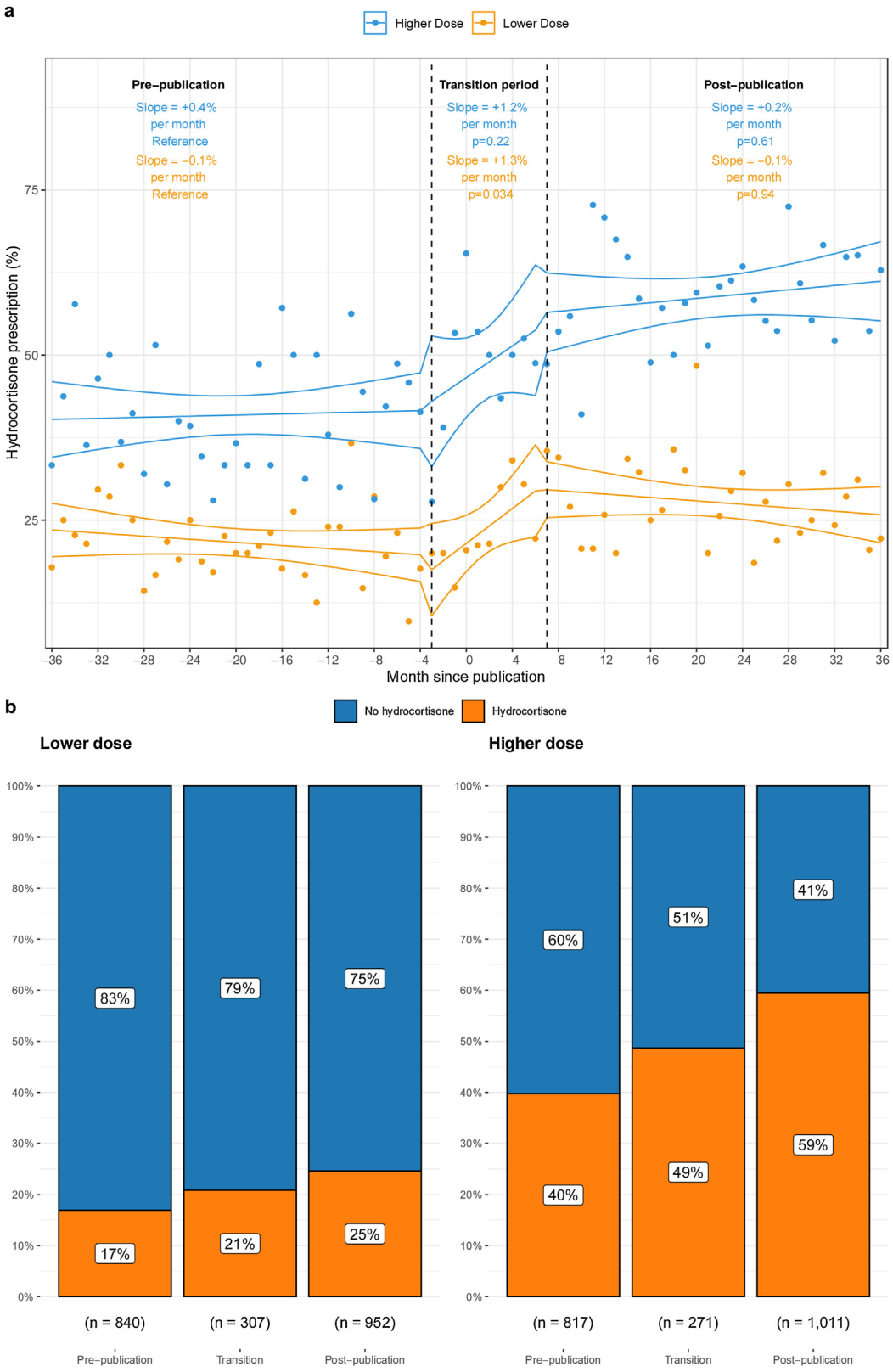

Fig. 2. Proportion of hydrocortisone given according to the Noradrenaline equivalent score category, a: linear regression of proportion evolution according to the publication period, b: crude proportion according to the publication period.
(a) Points represent the estimated proportion of hydrocortisone prescriptions with a 95% confidence interval in light-shaded areas. The lines represent the segmented linear regression of hydrocortisone prescription over time for each group with a 95% confidence interval of the fitted model in dark grey. *P*-value is calculated for the change in slope with respect to the Pre-publication period within each group

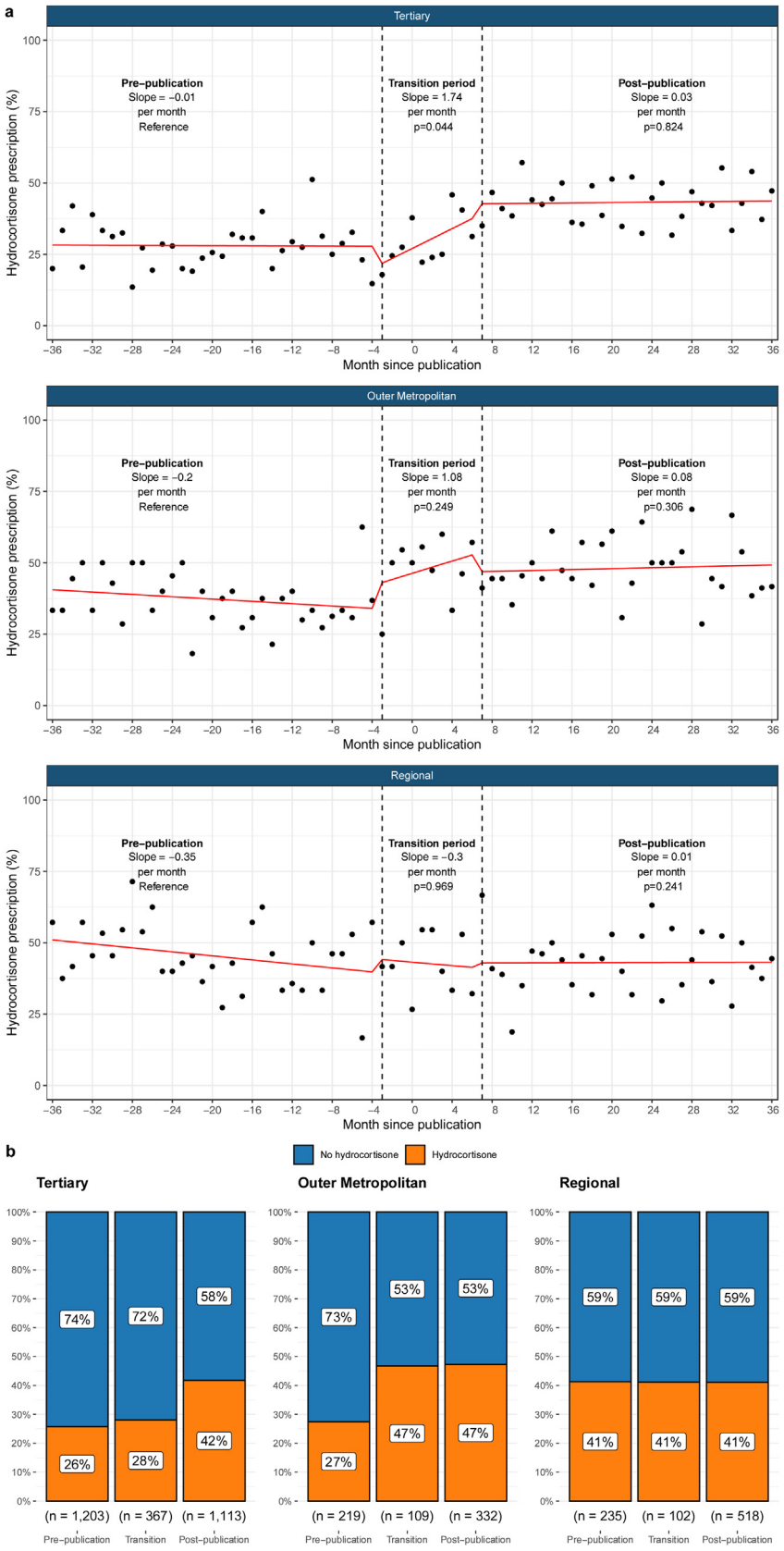

Fig. 3. Proportion of hydrocortisone given according to the site type, a: linear regression of proportion evolution according to the publication period, b: crude proportion according to the publication period.

Table 2
Factor associated with hydrocortisone prescription by unadjusted and multivariable logistic regression.

	Unadjusted				Multivariable		
Variables	N	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	*p*-value
Noradrenaline equivalent score category	4 198						
High		–	–		–	–	
Low		0.26	0.23 to 0.30	<0.0001	0.31	0.27 to 0.36	<0.0001
AKI Stage	4 198						
0		–	–		–	–	
1		1.59	1.34 to 1.89	<0.0001	1.44	1.20 to 1.73	0.0001
2		2.35	1.94 to 2.84	<0.0001	1.78	1.45 to 2.19	<0.0001
3		3.19	2.63 to 3.86	<0.0001	2.15	1.74 to 2.65	<0.0001
Peak lactate on the sepsis diagnosis day, per mmol/L	4 186	1.08	1.06 to 1.10	<0.0001	1.03	1.01 to 1.05	0.0012
Age, per year	4 198	1.01	1.00 to 1.01	0.0045	1.00	1.00 to 1.01	0.41
Site type	4 198						
Tertiary		–	–		–	–	
Outer Metropolitan		1.41	1.18 to 1.67	0.0001	1.27	1.05 to 1.53	0.016
Regional		1.44	1.23 to 1.68	<0.0001	1.24	1.04 to 1.48	0.017
Immunosuppression	4 198	1.54	1.26 to 1.88	<0.0001	1.60	1.28 to 2.01	<0.0001
APACHE III Score	4 197	1.01	1.00 to 1.01	<0.0001	1.00	1.00 to 1.01	0.043
Period since publication	4 198						
Pre-publication		–	–		–	–	
Transition		1.31	1.07 to 1.60	0.010	1.42	1.14 to 1.77	0.0015
Post-publication		1.89	1.64 to 2.17	<0.0001	2.03	1.74 to 2.36	<0.0001

[1] OR = Odds Ratio, CI = Confidence Interval.

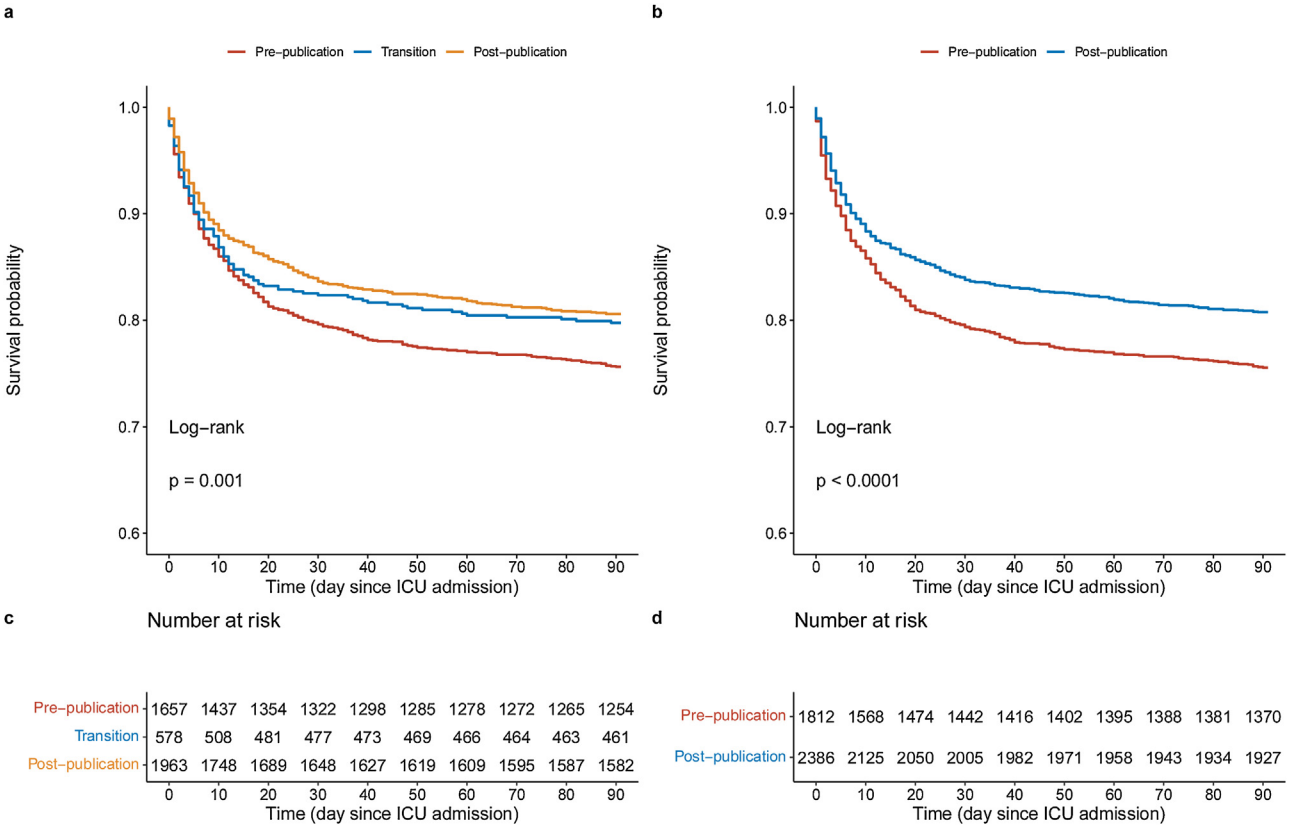

Fig. 4. Kaplan–Meier curves of 90-day mortality according to the publication period.

independently associated with a reduction in ICU length of stay (−1.2 days; 95% CI −2.2 to −0.18; $p = 0.021$). In contrast, regression models for additional secondary outcomes, ICU and hospital mortality, days alive and free of invasive mechanical ventilation at 28 days, and days alive and free of vasopressors at 28 days, did not demonstrate improved outcomes with the administration of hydrocortisone (Supplementary Methods Table S7 and Table S8).

Discussion

Key points

Our study, which analysed the change in hydrocortisone administration in nearly 5,000 patients with septic shock and examined how clinical practice changes over time in relation to the publication of the ADRENAL trial has several important findings.

Table 3
Hydrocortisone prescription and clinical outcomes.

Variable	N	Overall N = 4 198	Pre-publication N = 1 812	Post-publication N = 2 386	Hydrocortisone effect aOR (95%CI)	*p*-value
Hospital mortality	4 198	744 (18)	376 (21)	368 (15)	0.77 0.57 to 1.05	0.10
ICU mortality	4 198	564 (13)	288 (16)	276 (12)	0.76 0.54 to 1.06	0.10
90 days mortality	4 198	902 (21)	443 (24)	459 (19)	**aHR (95%CI)** 0.81 0.65 to 0.99	0.044
Days alive and ventilation free day 28	4 198	25 (17–28)	24 (15–28)	25 (18–28)	**β (95%CI)** −0.38 −0.77 to 0.01	0.055
Days alive and vasopressor free day 28	4 198	26 (21–28)	26 (21–28)	26 (22–28)	−0.84 −1.7 to −0.02	0.045
Hospital LOS among survivors (days)	3 454	12 (6–22)	13 (7–24)	11 (5–21)	0.67 −0.58 to 1.9	0.29
ICU LOS among survivors (days)	3 454	3.0 (1.0–6.0)	3.0 (2.0–7.0)	3.0 (1.0–6.0)	−1.2 −2.2 to −0.18	0.021

Descriptive statistics are presented as n (%) or median (p25-p75).
Adjusted estimates for Hydrocortisone effect was fitted by multivariable logistic regression, Cox model or quantile regression as appropriate. Covariables included in the model were APACHE III score, Noradrenaline equivalent score, Age, peak lactate on the day of sepsis diagnosis, site type, comborbidities, study period with an interaction term between the study period and the hydrocortisone prescription.
Abbreviations: aOR, Adjusted Odds Ratio; ICU, Intensive Care Unit; aHR, Adjusted Hazard Ratio; LOS: Length of stay.

Firstly, the proportion of patients with septic shock receiving IV hydrocortisone increased over time. Second, there were two breakpoints over time 3 months before and 6 months after publication. Third, despite the increase over time, as of the study's end date, less than half of patients with septic shock received IV hydrocortisone. Fourth, the use of fludrocortisone remained very limited at the study sites. Fifth, both the type of ICU and the vasopressor dose significantly impacted hydrocortisone administration over time. Finally, after adjusting for the severity of illness, hydrocortisone use significantly reduced ICU length of stay and 90-day mortality.

Relationship to literature

No previous study has examined the change in hydrocortisone usage in critically ill patients with septic shock, and no study has examined the impact of the ADRENAL trial publication on the use of hydrocortisone. Previous research has examined the implementation, or de-implementation, of other critical care therapies related to the publication of pivotal clinical trial evidence. Salter *et al.,* examined temperature management in patients after out-of-hospital cardiac arrest and the temporal trends related to the TTM trial, demonstrating an increase in the average lowest temperature in the first 24 h after a cardiac arrest [30]. Mackle *et al.,* examined oxygen therapy in critically ill patients after the publication of the ICU-ROX trial, demonstrating a reduction in average FiO2 in ICU-ROX sites [31].

Implications of study findings

Our study demonstrated that the publication of the ADRENAL trial was associated with a change in practice in Queensland ICUs. Of note, we did not demonstrate a change directly related to the publication of the ADRENAL trial; instead, we identified two break points three months before and six months after the publication of ADRENAL. Though the regional and temporal relationships suggest ADRENAL was associated with a change in practice, it is possible the APROCCHSS trial [32], which was co-published with ADRENAL, or international guidelines, that recommend steroid use in septic shock [33], were influential in altering prescribing practices. Furthermore, the change in steroid prescription three months before ADRENAL publication, as opposed to immediately after publication, may suggest alternative influences, such as international guidelines, the early online publication of ADRENAL, or other unknown factors.

The ADRENAL trial did not demonstrate an improvement in the primary patient-centred outcome of 90-day mortality. Instead, the potential beneficial effect was seen in the secondary outcomes of time to resolution of shock and time to discharge from the ICU. Therefore, if the temporal changes in hydrocortisone administration demonstrated in our study were influenced by the ADRENAL trial, clinicians placed significant value on improving these secondary outcomes. This 'paradox' is interesting as clinicians potentially change prescribing behaviour based on the results of a "negative" trial for the primary outcome of survival. It may be partly why only approximately ½ of the patients were treated with hydrocortisone post-ADRENAL publication.

Our study, of 4,198 patients, had a similar number of participants as the ADRENAL trial. In contrast to ADRENAL, and after adjusting for severity of illness and temporal changes in hydrocortisone use, the administration of hydrocortisone was associated with a decreased risk of 90-day mortality. The significance of this result in an observational cohort and when other patient-centred outcomes did not show a benefit for hydrocortisone is uncertain. However, this finding is unlikely to counter prevailing trends of increased hydrocortisone prescription and may provide a rationale for usage in all patients with septic shock.

The administration of steroids varied across different types of ICUs. Outer metropolitan and regional ICUs had a higher percentage of patients receiving steroids throughout the study period. However, only tertiary ICUs showed a significant change in steroid administration over time. The increased use of steroids in tertiary ICUs may be due to lower baseline usage or differences in ICU capacity [34].

Lastly, this study has demonstrated the utility of using highly granular, routinely collected data to examine the implementation or de-implementation of critical care therapies based on disseminating evidence-based research. This will allow for a thorough assessment of the impact of critical care research and examining variables related to the translation, or lack thereof, of clinical evidence in critically ill patients.

Strengths and limitations

Our study has several strengths. First, the cohort was sampled from a large, diverse number of ICUs responsible for providing ICU care to most of the patients with septic shock in Queensland. Second, the data was highly granular and comprised validated data extracted directly from the ICU electronic medical record used at all participating sites. Third, we utilised established techniques to identify patients with septic shock in routinely collected data. Fourth, our inclusion and exclusion criteria mirrored those of the ADRENAL trial, enhancing the validity of our results.

We acknowledge some limitations. First, this is an observational study with inherent limitations. Therefore, no direct causal inferences can be drawn from the findings, and the associations demonstrated are hypothesis-generating only. Second, the study did not demonstrate a clear breakpoint at the publication of ADRENAL, raising the possibility other factors were responsible for the change in practice. However, the sharp increase in hydrocortisone usage during the transition phase would suggest a temporal relationship. Third, most of the sites included in this study recruited patients to the ADRENAL trial, and the lead author of ADRENAL was based at one study site, therefore, there may be other non-clinical factors influencing the use the hydrocortisone in patients with septic shock. Fourth, due to most sites recruiting to ADRENAL, the period examined before the publication of ADRENAL may have included patients enrolled in the trial. To mitigate this, we conducted a sensitivity analysis, excluding the sites by the date of the last patient randomised, and demonstrated similar conclusions. Lastly, the source of sepsis was unknown in our cohort. Given the known benefit of steroids in severe pneumonia, this may be a confounder not accounted for in our analysis.

Conclusion

Our findings suggest that the publication of the ADRENAL trial changed clinical practice in Queensland ICUs, with clinicians increasing the use of hydrocortisone for patients with septic shock. Furthermore, the dose of vasopressor and the ICU type were associated with an increased proportion of patients receiving hydrocortisone. Finally, after adjusting for confounders and temporal changes in prescribing, hydrocortisone was associated with a reduction in 90-day mortality.

Author contributions

The study conception and design (KW, MR, AT, KL); data acquisition (KW); analysis (KW, AC); interpretation of data (all authors); article drafting (KW, MR, AT, KL), article revision for important intellectual content (all authors); final approval of the version submitted for publication (all authors); agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved (KW, MR < AT, KL).

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Statement of ethics

This study was approved by the Metro South Hospital and Health Service Human Research Ethics Committee (HREC/2022/QMS/82024), and an individual waiver of consent was granted.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Data availability statement

Data cannot be shared publicly due to institutional ethics, privacy, and confidentiality regulations. Data released for research under Sect. 280 of the Public Health Act 2005 requires an application to the Director-General of Queensland Health (PHA@health.qld.gov.au).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2024.101435.

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