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Hydrocortisone-associated death and hospital length of stay in patients with sepsis: A retrospective cohort of large-scale clinical care data☆

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ABSTRACT

Purpose: Sepsis is one of the leading causes of morbidity and mortality worldwide with approximately 50 million annual cases. There is ongoing debate on the clinical benefit of hydrocortisone in the prevention of death in septic patients. Here we evaluated the association between hydrocortisone treatment and mortality in patients diagnosed with sepsis in a large-scale clinical dataset.
Methods: Data from patients between 2008 and 2019 were extracted from the retrospective Medical Information Mart for Intensive Care IV (MIMIC-IV) database. Patients who received hydrocortisone after diagnosis were matched using propensity-score matching with patients who did not, to balance confounding (by indication and contraindication) factors between the groups. 90-day mortality and survivors' length of hospital stay was compared between patients who did or did not receive hydrocortisone.
Results: A total of 31,749 septic patients were included in the study (mean age: 67, men: 57.3%, in-hospital mortality: 15.6%). 90-day mortality was higher among the 1802 patients receiving hydrocortisone when compared with the 6348 matched non-users (hazard ratio: 1.35, 95% CI: 1.24–1.47). Hydrocortisone treatment was also associated with increased in-hospital mortality (40.9% vs. 27.6%, $p < 0.0001$) and prolonged hospital stay in those who survived until discharge (median 12.6 days vs. 10.8 days, $p < 0.0001$). Stratification for age, gender, ethnicity, occurrence of septic shock, and the need for vasopressor drug administration such as (nor) epinephrine did not reveal sub-population(s) benefiting of hydrocortisone use.
Conclusion: Hydrocortisone treatment is associated with increased risk of death as well as prolonged hospital stay in septic patients. Although residual confounding (by indication) cannot be ruled out completely due to the observational nature of the study, the present study suggests clinical implication of hydrocortisone use in patients with sepsis.

1. Introduction

Sepsis is a heterogeneous syndrome that can be initiated by any type of infection, including bacteria, viruses, fungi, and parasites. It affects about 50 million people globally each year and is one of the most common causes of mortality worldwide [1]. The current worldwide consensus definition of sepsis is "a life-threatening organ dysfunction caused by a host's dysregulated response to infection" [2].

The conventional approach to treat sepsis is source control through antibiotics and supporting failing organs through fluid resuscitation, vasoactive medication and mechanical organ support [3]. However, this approach does not adequately address the dysregulated host's immune

☆ Take home message: In retrospective analysis of real-world clinical data, no evidence was found for therapeutic value of corticosteroids in patients with sepsis. Instead we report that hydrocortisone treatment is associated with increased risk of death and length of stay in hospital in septic patients.

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response during sepsis, and therefore immune- and coagulation-based therapeutic strategies have been proposed [4,5]. To taper the pro-inflammatory host response in sepsis, corticosteroids have been administered in the treatment for septic shock patients for the past four decades [6,7]. Corticosteroids have broad effects on various cell systems including a very potent suppression of the immune response, while they may also boost blood pressure and glomerular filtration rate. Yet, recent discoveries provide impetus to reevaluate this approach; this includes the observation that the adaptive immune system is, in certain phases of the septic period, found to be in a state of marked immune suppression despite a generally active innate immune system [8]. In addition, suppressing the inflammatory host response with glucocorticoids allows secondary, nosocomial, infections to become an additional problem [9]. Consequently, clinical trials with short- and long-term mortality as primary outcome have shown either benefit or no clear impact [10–12].

Here we conducted a retrospective cohort study based on a large publicly available dataset to evaluate the association between hydrocortisone use and 90-day mortality and hospital stay in survivors in patients diagnosed with sepsis.

2. Materials and methods

2.1. Data source

A retrospective analysis was conducted using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database 1.0 containing clinical data of 523,740 ICU admitted individuals with critical illness in Beth Israel Deaconess Medical Center between 2008 and 2019 [13].

2.2. Patient population and data extraction

Fig. 1 shows the flowchart for the selection procedure of the study population. Sepsis was diagnosed according to the Third International Consensus Definition for sepsis and septic shock (also referred as Sepsis-3) [2]. Using Postgre SQL 10.0, data of patients who met the sepsis-3 criteria (n = 35,010) were extracted from the MIMIC-IV database. Repeated ICU admissions (n = 3027) and/or patients receiving oral hydrocortisone (n = 234) before admission were excluded from further analysis. Extracted variables included sex, age, ethnicity, pre-existing comorbidities including diabetes, chronic pulmonary disease (symptomatic dyspnea caused by chronic pulmonary dysfunction, including asthma and COPD), severe liver disease (cirrhosis and portal hypertension with variceal bleeding history), adrenal insufficiency (primary and drug-induced adrenal insufficiency, and other unspecified adrenal insufficiency), cancer, congestive heart failure, AIDS, clinical severity score (SAPSII, APSIII, SOFA) at day of admission, occurrence of septic shock, administration of vasoactive medication (epinephrine, norepinephrine, dopamine, phenylephrine) during hospitalization, the use of intravenous hydrocortisone during hospitalization, the need for invasive mechanical ventilation, time of entering and leaving the hospital, time of entering and leaving the intensive care unit (ICU), and date of death. Patients who received intravenous hydrocortisone while hospitalized were assigned to the hydrocortisone group (n = 1882), others were assigned to the non-hydrocortisone group (n = 29,867).

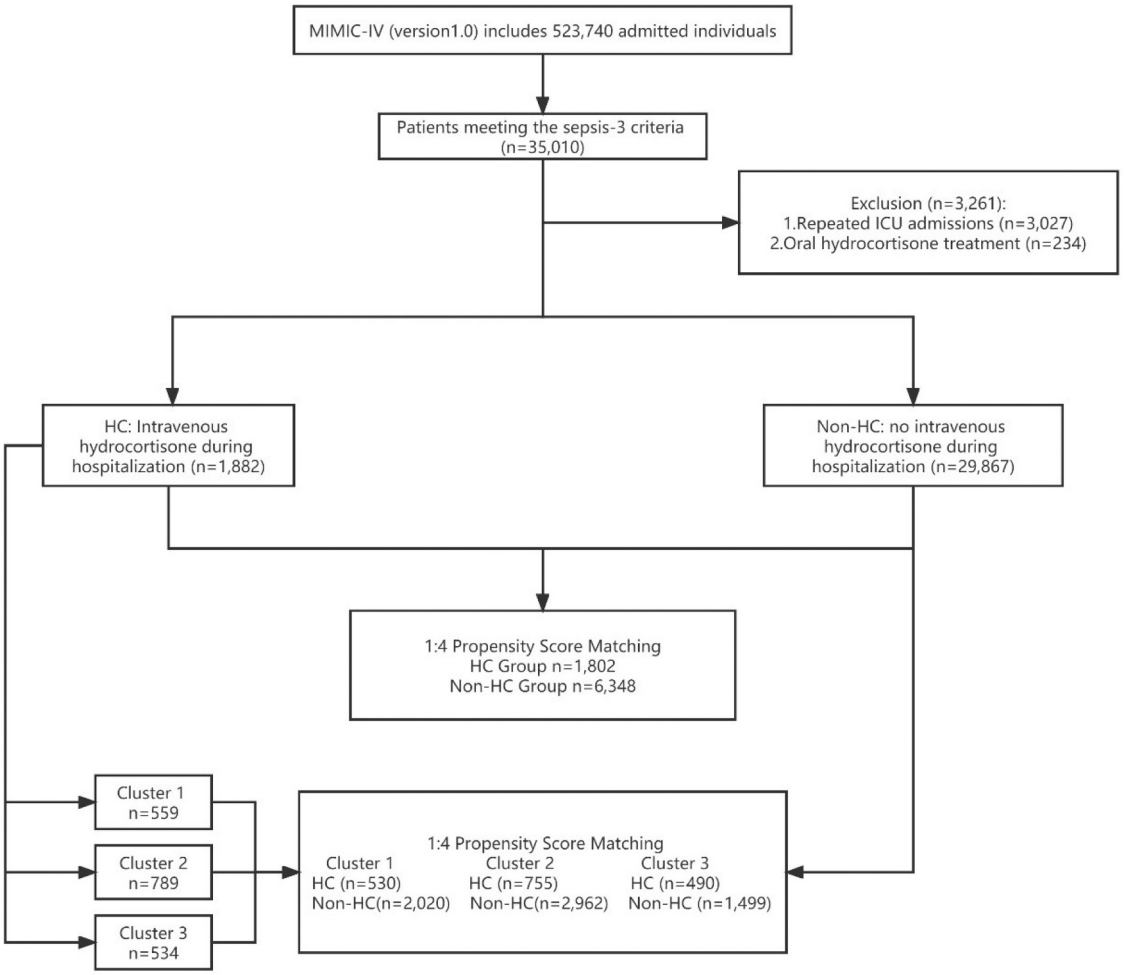

Fig. 1. The flowchart of selection procedure of study population. Data were retrieved from MIMIC-IV database.

2.3. Statistical analysis

Normally distributed continuous variables are reported as mean (SD) while non-normally distributed continuous variables are reported as median (Q25,Q75); categorical variables are presented as number with percentage and analyzed by Chi-Square test. Kaplan Meier curves with the Wilcoxon log-rank test and a univariable cox regression model were utilized for 90-day mortality. To address potential residual imbalances in the baseline covariates, additional multivariable-adjusted cox regression models were employed for 90-day mortality rate including the same baseline covariates that were also included in the PSM. Length of stay in hospital and ICU was log transformed (natural logarithm) for statistical analysis but presented as absolute numbers.

Propensity score (PS) matching (PSM) was conducted using R software 4.1.2 with 'MatchIt' package to balance groups for potential confounding factors (i.e., gender, age, ethnicity, APS-III score, SAPS-II score, SOFA score, chronic kidney disease, congestive heart failure, chronic pulmonary disease, diabetes mellitus, cancer, severe liver disease, AIDS, septic shock, adrenal insufficiency, invasive ventilation, epinephrine, dopamine, norepinephrine, phenylephrine) by matching nearest neighbors using a caliper of 0.05 standard deviation of the logit of the estimated propensity score. All the variables employed in PSM and multivariable-adjusted cox regression model were baseline characteristics. PSM was repeated after adding length of stay to the model, and after stratifying for the occurrence of septic shock. Each patient of the hydrocortisone group was matched with a maximum of four patients of the non-hydrocortisone group. Patients were only included once within the analysis. If the standardized mean difference (SMD) is less than 0.10, the covariate was considered balanced between users and nonusers of hydrocortisone [14]. Inverse probability of treatment weighting (IPTW) [15], which is another PS-based adjustment, was used for further validation. The PS for each patient was calculated from logistic regressions including the baseline characteristics used for PSM. We applied the 1/PS as a weight for the hydrocortisone group, and the 1/(1-PS) for the non-hydrocortisone group.

To characterize septic patients who were treated with hydrocortisone and identify potential subgroups of patients that may benefit of hydrocortisone treatment, a full Bayesian latent variable model was constructed using a R package named iClusterBayes that can jointly cluster continuous and discrete data in R software 4.1.2 with 'MOVICS' package [16]. Clusters of patients were identified by minimizing the Bayesian information criterion. PSM was again applied on the identified clusters to match patients who received hydrocortisone to patients who did not.

GraphPad Prism 9.0 was used to create graphs. A two-sided p-value < 0.05 was considered statistically significant. Graphical abstract was created with BioRender.com.

3. Results

3.1. Hydrocortisone use in patients with sepsis

Out of the 31,749 patients who met the sepsis-3 criteria and other inclusion criteria for this study, 1882 patients were assigned to the hydrocortisone group and 29,867 to the non-hydrocortisone group. Characteristics of these groups are depicted in Table 1. Patients of the hydrocortisone ('HC') group received a median daily dose of 200 (104, 400) mg for a median duration of 2 (1, 4) days and had higher clinical scores for APSIII, SAPSII, and SOFA when compared to septic patients of the non-hydrocortisone ('non-HC') group. Among the patients who received hydrocortisone, the occurrence of comorbidities was also more common. The majority of patients who received hydrocortisone therapy additionally received norepinephrine (HC 69.1% vs non-HC 28.2%) and were dependent on invasive mechanical ventilation (HC 65.3% vs non-HC 48.0%).

3.2. Higher mortality among patients with sepsis receiving hydrocortisone

In the group of patients who received hydrocortisone, 90-day mortality was higher (unadjusted cox regression hazard ratio [HR]: 2.27, 95% CI: 2.11–2.45; multivariable-adjusted cox regression HR:1.25, 95% CI: 1.16–1.36; Fig. 2A). In addition, in-hospital mortality was higher

Table 1
Characteristics and propensity score matching.

		Before PSM			After PSM		
	Cohort (n = 31,749)	**non-HC (n = 29,867)**	**HC (n = 1882)**	**SMD**	**non-HC (n = 6348)**	**HC (n = 1802)**	**SMD**
Gender (% male)	57.3%	57.6%	53.5%	0.082	53.7%	53.7%	0.008
Age	67 ± 16	67 ± 16	65 ± 15	0.101	66 ± 16	65 ± 15	0.001
Ethnicity (% white)	67.5%	67.6%	66.2%	0.031	65.8%	66.2%	0.016
APS-III	50(37,69)	49(36,67)	70(50,96)	0.658	66(48,90)	70(49,95)	0.010
SAPS-II	40 ± 14	39 ± 14	48 ± 17	0.554	46 ± 16	48 ± 17	0.012
SOFA score	3.6 ± 2.0	3.5 ± 1.9	4.7 ± 2.6	0.430	4.5 ± 2.5	4.6 ± 2.6	0.014
Chronic kidney disease (%)	25.0%	24.7%	28.8%	0.090	28.7%	28.4%	0.002
Congestive heart failure (%)	32.4%	32.1%	36.4%	0.089	36.0%	35.8%	0.006
Chronic pulmonary disease (%)	27.8%	27.5%	31.7%	0.090	31.8%	31.5%	0.009
Diabetes mellitus (%)	24.9%	24.9%	23.4%	0.037	23.5%	23.6%	0.008
Cancer (%)	13.7%	13.2%	21.8%	0.209	19.6%	21.2%	0.001
Severe liver disease (%)	7.6%	7.4%	10.7%	0.109	10.0%	10.7%	0.001
AIDS (%)	0.8%	0.8%	1.5%	0.061	1.2%	1.4%	0.000
Septic shock (%)	21.7%	19.7%	54.1%	0.692	48.4%	53.3%	0.012
Adrenal insufficiency (%)	0.4%	0.2%	4.9%	0.219	0.8%	2.0%	0.010
Invasive ventilation (%)	49.0%	48.0%	65.3%	0.362	61.7%	64.9%	0.010
Epinephrine (%)	6.2%	5.5%	17.1%	0.306	12.4%	16.4%	0.018
Dopamine (%)	4.0%	3.6%	9.1%	0.189	7.7%	8.9%	0.000
Norepinephrine (%)	30.6%	28.2%	69.1%	0.886	64.1%	67.9%	0.004
Phenylephrine (%)	26.7%	26.0%	38.0%	0.247	34.4%	37.7%	0.003

Definition of abbreviations: APS-III = Acute physiology Score; HC = hydrocortisone; non-HC = non-hydrocortisone; PSM = Propensity Score Matching; SAPS-II = Simplified Acute Physiology Score; SOFA = Sequential Organ Failure Assessment.
Patients who met the sepsis-3 criteria and were admitted to ICU for the first time, excluding those receiving oral hydrocortisone treatment, were included in the study. Patients who received intravenous hydrocortisone at any given time during their hospital stay were assigned to the HC group, others were assigned to the non-HC group. Each patient of the HC group was matched to max. 4 patients of the non-HC group using PSM. Normally distributed continuous variables are reported as mean (SD), other continuous variables as median (25%, 75%) and categorical variables as percentage.

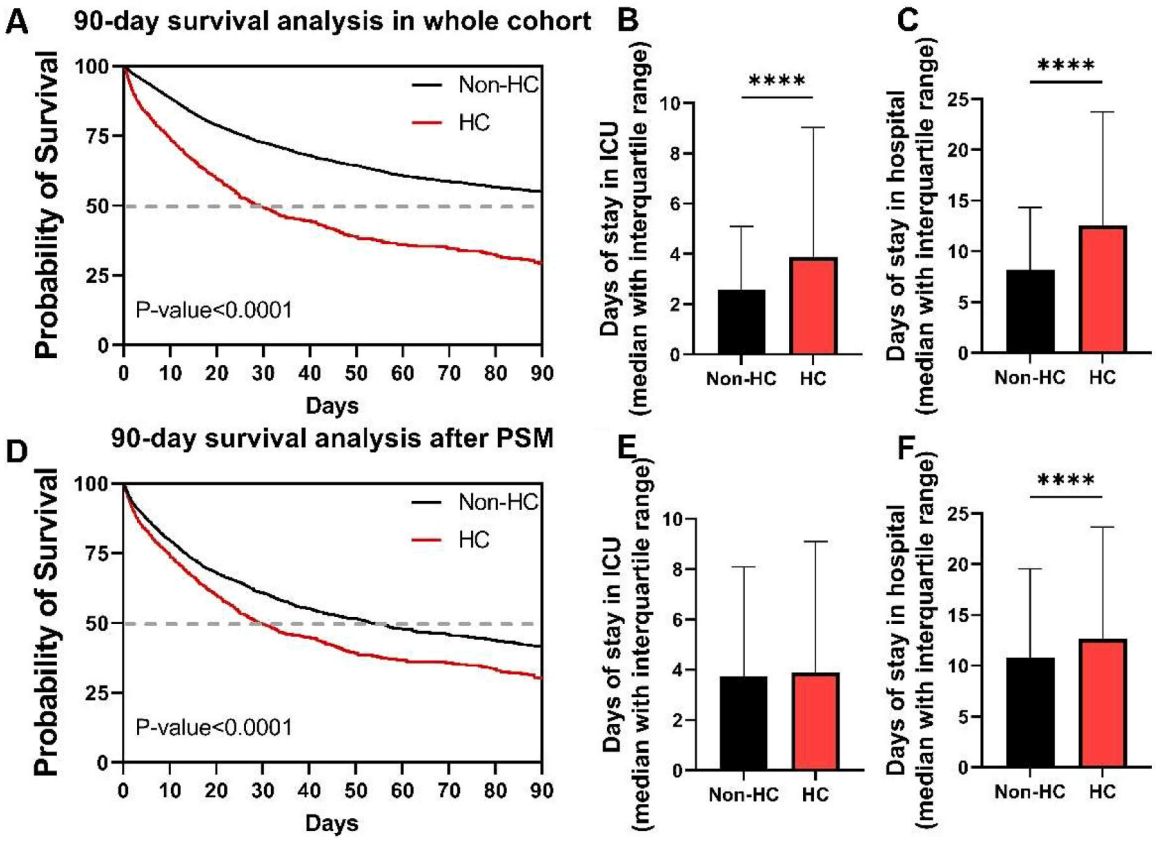

Fig. 2. Patients who met the sepsis-3 criteria were included in the study. Patients who received intravenous hydrocortisone at any given time during their hospital stay were assigned to the hydrocortisone (HC) group, others were assigned to the non-hydrocortisone (non-HC) group. A) 90-day survival curves for the whole cohort. Length of stay in B) intensive care unit (ICU) and C) hospital for those who survived. Each patient of the HC group was matched to max. 4 patients of the non-HC group using propensity score matching (PSM). D) 90-day survival, and length of stay in E) ICU and F) hospital after PSM. * ** *P-value< 0.0001.

among the patients receiving hydrocortisone (41.4% vs. 14.0%, $P < 0.0001$). Compared to patients who did not receive hydrocortisone, hydrocortisone users who survived had to stay for a longer period in ICU (median 3.9 vs. 2.6 days, $P < 0.0001$, Fig. 2B) and the hospital (median 12.6 vs. 8.2 days, $P < 0.0001$, Fig. 2C).

3.3. Hydrocortisone therapy is detrimental independent of clinical characteristics

To limit confounding-by-indication and -contraindication, each individual in the hydrocortisone group was matched to a maximum of four individuals of the non-hydrocortisone group (Fig. 1; Table 1). In total, 6348 patients of the non-hydrocortisone group were identified as matches for 1802 hydrocortisone users, resulting in a standard mean difference lower than 0.10 for all variables indicating balance among the groups [14]. Even after balancing the groups by PSM (Fig. S1), leading to similar clinical characteristics between both groups, patients who received hydrocortisone had an increased 90-day mortality rate when compared to patients who did not receive hydrocortisone (unadjusted cox regression HR: 1.35, 95% CI: 1.24–1.47; multivariable-adjusted cox regression HR: 1.28, 95% CI: 1.17–1.39; Fig. 2D). In-hospital mortality also remained higher in the hydrocortisone group (40.9% vs. 27.6%, $P < 0.0001$). In survivors, hydrocortisone treatment was associated with prolonged need for norepinephrine treatment (median 1.6 vs. 1.3 days, $p < 0.0001$). In addition, survivors' length of stay in the ICU was not different between the groups (median 3.9 vs. 3.7 days, $P = 0.114$, Fig. 2E), and length of stay in the hospital was increased for patients in the hydrocortisone group (median 12.6 vs. 10.8 days, $P < 0.0001$, Fig. 2F). Additionally, after adjustment by IPTW, hydrocortisone use remains associated with higher 90-day mortality rate (Fig. S2).

Although length of stay in the ICU was not different between patients who did or did not receive hydrocortisone, it is still possible that patients who stay longer in the ICU are more likely to receive hydrocortisone at some point. Therefore we repeated the PSM and included length of stay in the ICU as potential confounding factor in the model. In this additional analysis, 6538 patients of the non-hydrocortisone group were identified as matches for 1798 hydrocortisone users (Table S1, Fig. S3). Patients who received hydrocortisone exhibited a higher 90-day mortality rate (unadjusted cox regression HR: 1.39, 95% CI: 1.28–1.52; multivariable-adjusted cox regression HR: 1.30, 95% CI: 1.19–1.42; Fig. S4) and in-hospital mortality rate (40.9% vs. 27.4%, $P < 0.0001$) compared to matched patients who did not receive hydrocortisone. Hydrocortisone use remains associated with higher 90-day mortality rate after adjustment by IPTW (Fig. S5).

3.4. No benefit of hydrocortisone therapy in subgroup analysis

Stratified univariate cox regression analysis was used to potentially identify subgroups of patients benefiting of hydrocortisone administration. However, hydrocortisone administration was not associated with lower mortality risk in any of the subgroups before and after PSM (Fig. 3).

As another approach to identify subgroups of patients who might benefit of hydrocortisone administration during sepsis, a Bayesian model was constructed to better define the characteristics of patients who received hydrocortisone (Fig. 4A). By doing so, three distinct clusters were defined by the used algorithm. Cluster 1 showed the lowest mortality rate, and patients within this cluster were typically of younger age, and had lower SAPS-II score with less preexisting comorbidities. Cluster 2 was characterized by an intermediate mortality rate and

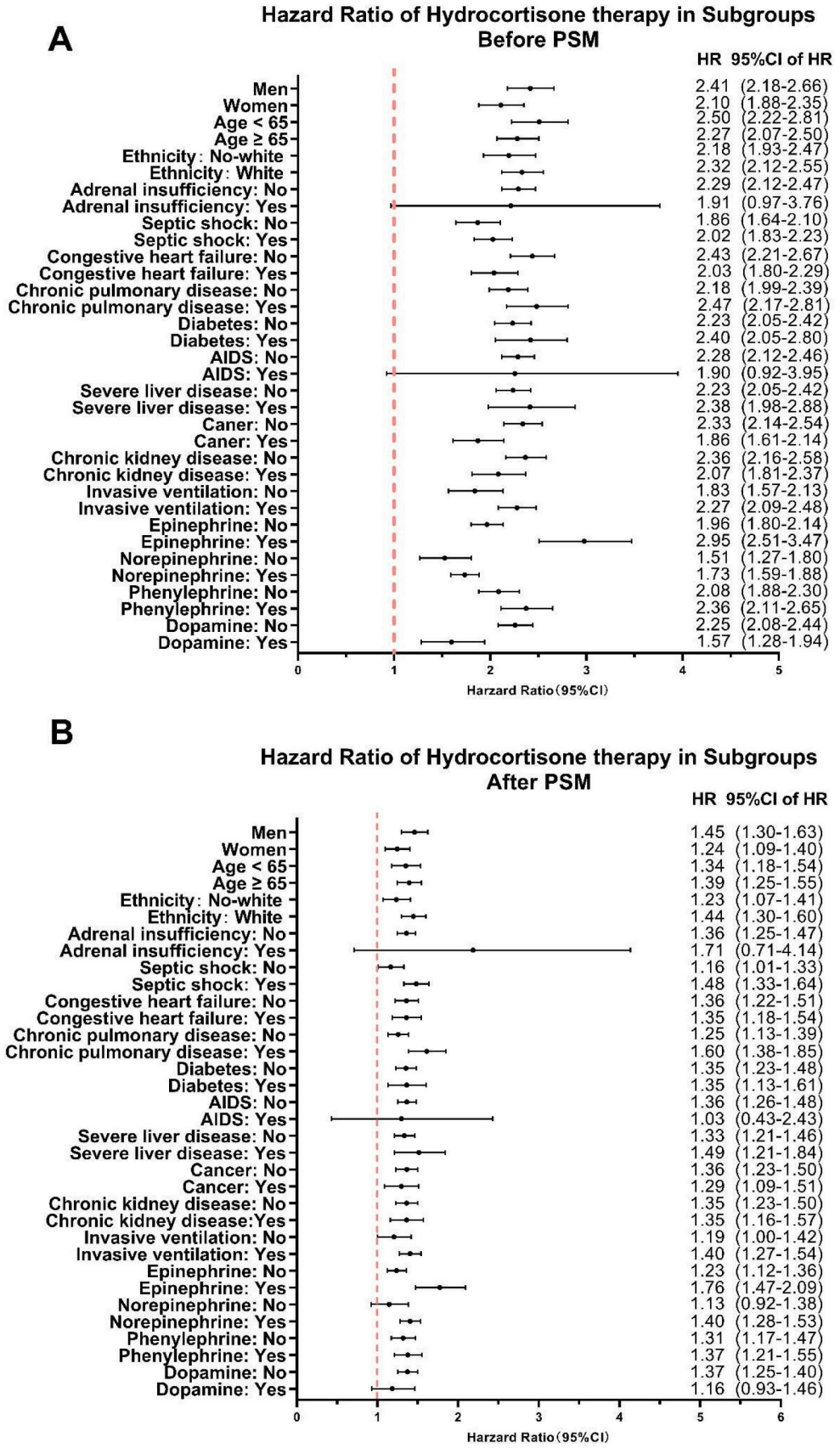

Fig. 3. Patients who met the sepsis-3 criteria were included in the study. Patients who received intravenous hydrocortisone at any given time during their hospital stay were assigned to the hydrocortisone (HC) group, others were assigned to the non-hydrocortisone (non-HC) group. Each patient of the HC group was matched to max. 4 patients of the non-HC group using propensity score matching (PSM). Cox regression analysis was performed to calculate hazard ratios following hydrocortisone therapy in subgroups A) before PSM, and B) after PSM.

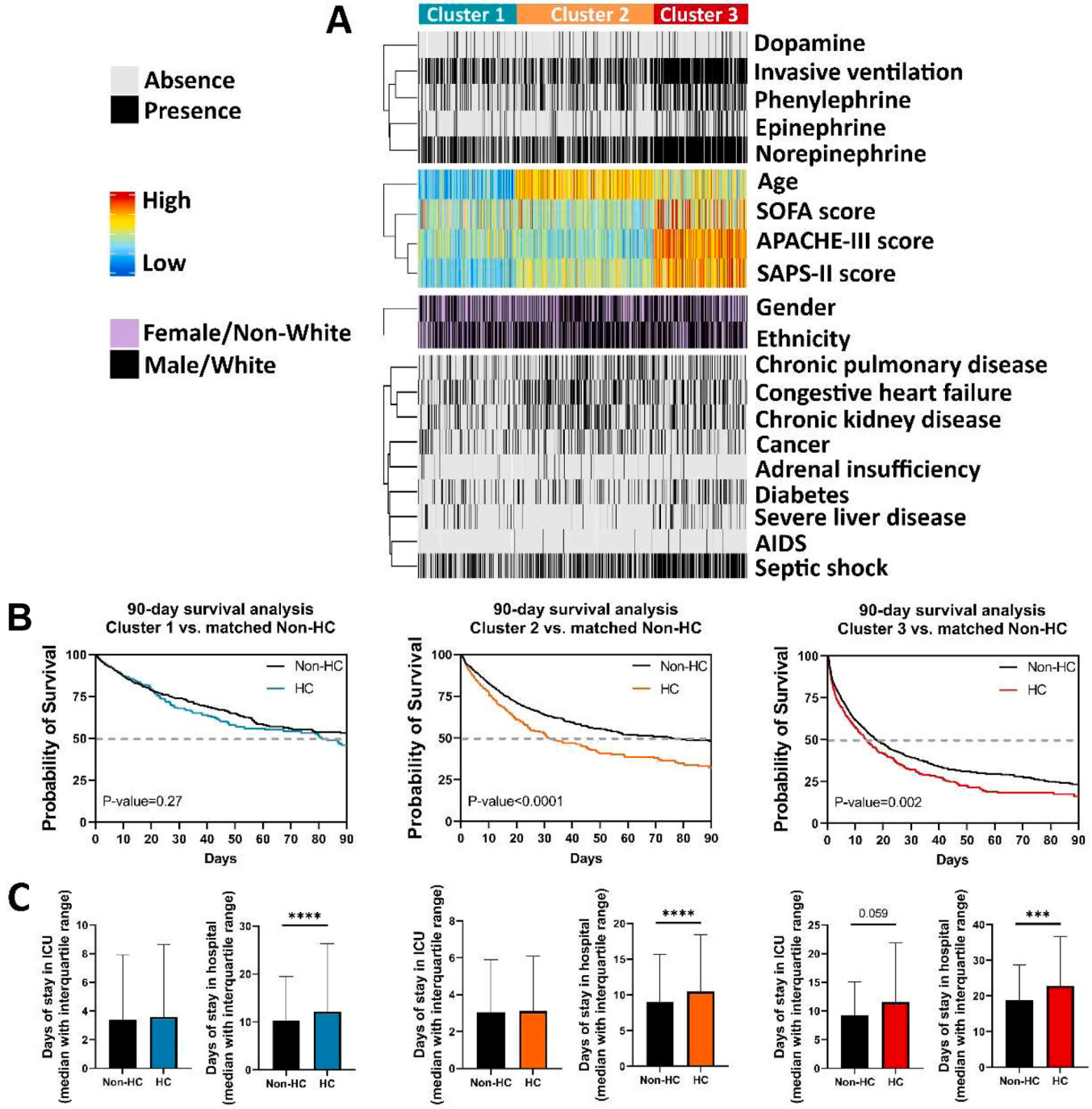

Fig. 4. Patients who met the sepsis-3 criteria were included in the study. Patients who received intravenous hydrocortisone at any given time during their hospital stay were assigned to the hydrocortisone (HC) group, others were assigned to the non-hydrocortisone (non-HC) group. A) For patients of the HC group a Bayesian latent variable model was constructed to identify three distinct clusters. For each cluster, each patient was matched to max. 4 patients of the non-HC group using propensity score matching (PSM). B) 90-day survival, and C) length of stay at hospital and ICU after PSM. *P-value< 0.05, * ** *P-value< 0.0001.

comprised more patients of older age and higher number of preexisting comorbidities. Patients within cluster 3 had an extremely poor prognosis as indicated by high APACHE-III, SAPS-II and SOFA scores, and were more often diagnosed with septic shock. PSM was applied separately for each cluster to match patients receiving hydrocortisone to those with comparable clinical characteristics but not receiving hydrocortisone. With the exception of cluster 1 (unadjusted cox regression HR 1.11, 95% CI: 0.92–1.35; multivariable-adjusted cox regression HR: 1.41, 95% CI: 1.15–1.73), hydrocortisone use was associated with higher mortality in cluster 2 (unadjusted cox regression HR: 1.46, 95% CI: 1.27–1.68; multivariable-adjusted cox regression HR: 1.82, 95% CI: 1.58–2.10) and 3 (unadjusted cox regression HR: 1.21, 95% CI: 1.07–1.38; multivariable-adjusted cox regression HR: 1.14, 95% CI: 1.01–1.30). Hydrocortisone therapy was associated with prolonged stay in the hospital among the survivors (Fig. 4C) and increased in-hospital mortality (Cluster 1: HC 24.9% vs. Non-HC 16.9%; Cluster 2: HC 33.5% vs. Non-HC 21.6%; Cluster 3: HC 68.7% vs. Non- HC 55.9%) in all clusters.

As current international guidelines only suggest the use of intravenous corticosteroids for adults with septic shock, we next repeated PSM after selecting for patients with septic shock. Of the 6906 patients with

septic shock, 1020 patients received hydrocortisone. To create groups balanced for confounders, each individual in the hydrocortisone group was matched to one individual of the non-hydrocortisone group, yielding 968 matches (Table 2, Fig. S6). In this subgroup analysis, hydrocortisone use remained associated with higher 90-day mortality before (unadjusted cox regression HR: 2.02, 95% CI: 1.83–2.23; multivariable-adjusted cox regression HR: 1.28, 95% CI: 1.16–1.43; Fig. 5A) and after PSM (unadjusted cox regression HR: 1.27, 95% CI: 1.12–1.45; multivariable-adjusted cox regression HR: 1.33, 95% CI: 1.17–1.52; Fig. 5D). In addition, there was no difference in length of stay in the ICU (Fig. 5E) or hospital (Fig. 5F) between patients who did or did not receive hydrocortisone treatment. Moreover, the in-hospital mortality rate was higher among those who received hydrocortisone therapy when compared to matched patients who did not receive hydrocortisone (50.52% vs. 39.15%, $p < 0.0001$). The results remain consistent after performing IPTW (Fig. S7).

4. Discussion

For decades, hydrocortisone has been widely administered to patients with sepsis and refractory septic shock. In the current study, we analyzed retrospective data of 31,749 patients with sepsis of whom 5.7% received intravenous hydrocortisone while hospitalized, and revealed that hydrocortisone treatment is associated with higher 90-day mortality, increased in-hospital mortality and prolonged survivors' length of stay in the hospital. PSM was applied to balance confounding factors between patients who received hydrocortisone and those who did not, to limit confounding-by-indication. The data after PSM suggested that hydrocortisone therapy is detrimental independent of clinical characteristics.

Initial guidelines advocating the use of corticosteroids in septic shock were primarily based on the landmark study of Annane et al. [17] which concluded that a 7-day treatment with low doses of hydrocortisone and fludrocortisone reduced the risk of death in patients with septic shock and relative adrenal insufficiency without increasing adverse events. However, this study has been criticized for changing enrollment criteria during the trial and the high frequency of patients with an indication for hydrocortisone treatment due to adrenal insufficiency. The subsequent CORTICUS trial found no survival benefit for hydrocortisone, either overall, or in patients with adrenal insufficiency defined as an absence of a response to a corticotropin test [18]. In line with these data, recent meta-analyses concluded that for septic shock patients without adrenal insufficiency, low dose corticosteroids (200–300 mg hydrocortisone per day for around 7 days) does not improve survival and increases the risk of adverse events (e.g. ICU acquired bacteriemia, gastrointestinal bleeding, or shock relapse/shock), while it does reduce the duration of shock, mechanical ventilation and ICU stay [19,20]. Additionally, hydrocortisone may be associated with an increased risk of hypernatremia and muscle weakness while it is not associated with a reduced 90-day mortality rate [21]. We here report that hydrocortisone treatment actually is associated with reduced survival and generally a prolonged survivors' length of stay in the ICU. Only in a few subgroups, including those patients with preexisting adrenal insufficiency we observed no association between hydrocortisone treatment and mortality. These data should be interpreted with caution due to the low number of patients in these groups.

It is important to note that recommendations regarding the use of hydrocortisone have evolved over the past years. In 2004, the Survival Sepsis Campaign recommended the use of intravenous hydrocortisone in septic shock patients who require vasopressor therapy despite adequate fluid replacement [22]. However, since 2012 the guidelines [3,23,24] advise against the use of intravenous hydrocortisone in those who achieve hemodynamic stability with adequate fluid resuscitation and vasopressor therapy. Considering that the MIMIC-IV database encompasses clinical records from 2008 to 2019, the administration of hydrocortisone may have varied based on the prevailing guidelines at the time of data collection. Nevertheless, we observed a relatively equal distribution of hydrocortisone usage across the years, and even a significant number of patients receiving hydrocortisone without septic shock and with relatively low SOFA scores. Whilst we attempted to mitigate confounding factors through PSM and used stratification to specifically select patients with septic shock, we do acknowledge that inherent differences between patients receiving hydrocortisone therapy and those without cannot be completely eliminated.

Accordingly, a systematic review indicated that almost all clinical controlled trials on the use of corticosteroids in sepsis are at a high risk of selection bias, performance and detection bias, attrition bias and selective reporting [20,25]. In the current study, we addressed the use of hydrocortisone in a retrospective dataset and applied PSM to balance the groups for clinical characteristics and thereby reduce (residual) confounding (by indication and contraindication). The result of our attempt to generate well-matched groups of patients who did and who did not receive hydrocortisone, points in the direction that decision on choice of medication in sepsis treatment is not solely based on meeting specific criteria. Importantly, we found that hydrocortisone therapy was associated with higher 90-day mortality, higher in-hospital mortality and

Table 2
Characteristics and propensity score matching of patients with septic shock.

		Before PSM			After PSM		
	Septic shock (n = 6906)	non-HC (n = 5886)	HC (n = 1020)	SMD	non-HC (n = 968)	HC (n = 968)	SMD
Gender (% male)	55.5%	55.7%	54.8%	0.017	55.4%	55.3%	0.002
Age	68 ± 15	68 ± 15	66 ± 14	0.203	66 ± 16	66 ± 14	0.005
Ethnicity (% white)	68.0%	68.4%	65.9%	0.053	66.1%	65.9%	0.004
APS-III	64(48,87)	61(47,83)	80(58,106)	0.511	79(57,104)	58,105	0.008
SAPS-II	45.6 ± 15.6	44.4 ± 15.0	52.2 ± 17.0	0.455	51.7 ± 17.6	52.0 ± 16.6	0.141
SOFA score	4.4 ± 2.3	4.2 ± 2.2	5.1 ± 2.8	0.315	5.1 ± 2.7	5.1 ± 2.8	0.006
Chronic kidney disease (%)	30.5%	30.5%	30.2%	0.007	30.7%	30.5%	0.007
Congestive heart failure (%)	38.2%	38.0%	39.2%	0.024	38.4%	38.4%	0
Chronic pulmonary disease (%)	29.4%	29.1%	30.8%	0.036	31.9%	30.4%	0.034
Diabetes mellitus (%)	27.4%	27.9%	24.7%	0.074	25.3%	24.9%	0.010
Cancer (%)	16.3%	15.4%	21.5%	0.148	20.6%	21.2%	0.015
Severe liver disease (%)	9.5%	9.0%	12.3%	0.099	11.7%	12.4%	0.022
AIDS (%)	1.3%	1.1%	2.3%	0.077	2.0%	2.0%	0
Adrenal insufficiency (%)	0.9%	0.2%	4.4%	0.203	1.2%	1.1%	0.005
Invasive ventilation (%)	51.1%	47.9%	69.7%	0.475	67.5%	69.7%	0.050
Epinephrine (%)	6.8%	4.8%	18.7%	0.357	17.1%	17.4%	0.005
Dopamine (%)	6.1%	5.5%	9.6%	0.139	7.6%	9.3%	0.056
Norepinephrine (%)	68.2%	65.0%	86.8%	0.642	87.2%	86.1%	0.034
Phenylephrine (%)	26.8%	24.2%	41.3%	0.346	42.1%	41.3%	0.005

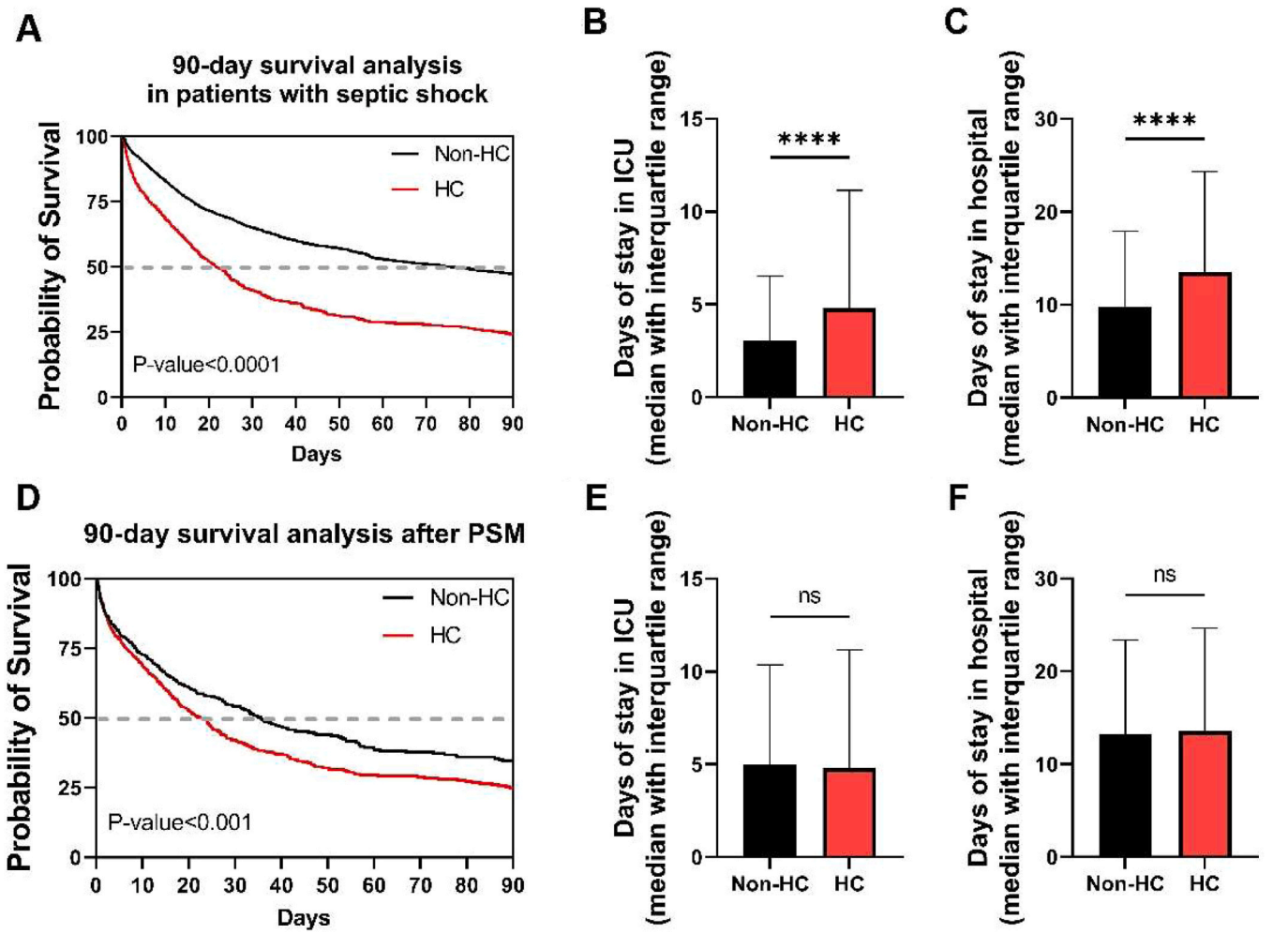

Fig. 5. Patients who met the sepsis-3 criteria and were diagnosed with septic shock were included in the study. Patients who received intravenous hydrocortisone at any given time during their hospital stay were assigned to the hydrocortisone (HC) group, others were assigned to the non-hydrocortisone (non-HC) group. A) 90-day survival curves for the whole cohort. Length of stay in B) intensive care unit (ICU) and C) hospital for those who survived. Each patient of the HC group was matched to a patient of the non-HC group using propensity score matching (PSM). D) 90-day survival, and length of stay in E) ICU and F) hospital after PSM. * ** *P-value< 0.0001.

reduced survival and prolonged survivors' length of stay in the hospital, raising concerns regarding the safety of hydrocortisone in the treatment of sepsis. Furthermore, cox proportional regression analyses did not reveal any subgroups benefiting of hydrocortisone use following clustering analyses.

As an alternative approach to identify subgroups benefiting of hydrocortisone use, unsupervised clustering analysis was performed on the data of patients receiving hydrocortisone while hospitalized. This clustering model offers a comprehensive and integrated method for categorizing septic patients since it can differentiate septic patients who have received hydrocortisone treatment by taking into account a broad range of clinical features, encompassing aspects of clinical treatment, comorbidities, geographical demographic characteristics, and clinical scores. This resulted in three distinct clusters of patients on which PSM was applied. Again, hydrocortisone did not improve clinical outcome in any of the clusters including a cluster of patients characterized by severe sepsis or septic shock.

Our study comes with some limitations, including the use of retrospective data, which generally has poor precision because it contains limited clinical data while the definition of symptoms and diagnosis varies depending on the experience of the physicians. Nevertheless, our data highlights the veritable effects of administering hydrocortisone to septic patients in real-world clinics. PSM was applied to balance the groups of patients who did or did not receive hydrocortisone for clinical characteristics, and even though we have tried to maximally include common characteristics that are applied in clinics to evaluate the prognosis of septic patients, we cannot fully exclude confounding-by-indication or -contraindication. This is possibly reflected in the fact that hydrocortisone treatment was associated with prolonged need for norepinephrine treatment in survivors, while hydrocortisone treatment is generally believed to accelerate shock reversal. Based on the current dataset we also cannot make any statements on the reasons for prescribing hydrocortisone. Other limitations are the use of data from a single center and the use of sepsis-3 criteria for inclusion, which is different from previous large randomized controlled trials.

Concluding, using a real-world clinical database we did not find evidence for therapeutic value of corticosteroids in patients with sepsis, and rather showed that hydrocortisone treatment is associated with increased risk of death and length of stay in hospital in septic patients. Importantly, the question remains if corticosteroids have any therapeutic value in subgroups of patients with sepsis at all, but we did not find evidence favoring this hypothesis. Prospective phase IV studies conducted in a real-world setting are needed to determine the effect of steroid use on outcome from sepsis in contemporary practice.

Ethical approval

The collection of patient information and creation of the MIMIC-IV dataset as research resource was reviewed by the Institutional Review Board at the Beth Israel Deaconess Medical Center, who granted a waiver of informed consent and approved the data sharing initiative.

CRediT authorship contribution statement

Mohan Li conception of the work, analysis and interpretation of data, drafting the work; Raymond Noordam, Patrick C.N. Rensen, Sander Kooijman conception of the work, interpretation of data, and critical review of the work. Elizabeth M. Winter, Matijs van Meurs, Hjalmar R. Bouma, M. Sesmu Arbous interpretation of data, and critical review of the work.

Declaration of Competing Interest

I, Mohan Li, hereby declare that there is no conflict of interest pertaining to the research work titled " Hydrocortisone-associated death and hospital length of stay in patients with sepsis: A retrospective cohort of large-scale clinical care data" submitted for consideration to be published in Biomedicine & Pharmacotherapy. Throughout the course of this research, no financial or non-financial relationships or activities that could potentially influence or bias the findings, interpretations, or conclusions of this work have been present. Additionally, there are no affiliations with any organization, company, or individual that might create a conflict of interest in connection with this research. I confirm that this Declaration of Interest is accurate and complete to the best of my knowledge.

Data availability

The authors do not have permission to share data.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2023.115961.

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