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Early Corticosteroid Exposure and Hospital Mortality in Critically Ill Patients With Cancer and Nonviral Pneumonia: A Target Trial Emulation

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Abstract

Purpose

Adjunctive corticosteroids reduce mortality in selected patients with severe community-acquired pneumonia, but their benefit in critically ill patients with cancer remains uncertain because this population is underrepresented in randomized trials. We emulated a target trial to evaluate early corticosteroid initiation and hospital mortality in critically ill adults with malignancy and nonviral pneumonia.

Methods

We emulated a target trial using MIMIC-IV among adults with active malignancy and nonviral pneumonia who remained alive and hospitalized 48 hours after ICU admission. Treatment strategies were corticosteroid initiation within 48 hours or no corticosteroids during this period. The primary outcome was hospital mortality. Propensity score-based IPTW was used for confounding adjustment, with prespecified sensitivity analyses using a 24-hour exposure window and propensity score matching.

Results

The landmark cohort included 2,227 patients, of whom 531 (23.8%) received early corticosteroids. The primary IPTW analysis included 2,160 complete cases. IPTW achieved adequate balance across all covariates in the primary propensity score model. Early corticosteroid initiation was not associated with hospital mortality (OR, 1.01; 95% CI, 0.80–1.27; *P* = 0.925). Findings were consistent after multivariable adjustment, propensity score matching, and alternative exposure definitions. Early corticosteroid initiation was associated with shorter hospital but not ICU length of stay or invasive mechanical ventilation duration.

Conclusion

Among critically ill adults with active malignancy and nonviral pneumonia, early corticosteroid initiation was not associated with hospital mortality. These findings do not support extrapolating evidence favoring adjunctive corticosteroids in selected patients with severe community-acquired pneumonia to critically ill patients with cancer.

INTRODUCTION

Acute respiratory failure secondary to pneumonia is among the leading causes of intensive care unit (ICU) admission in patients with cancer and is associated with substantial morbidity and hospital mortality, particularly among those requiring invasive mechanical ventilation (1). Respiratory infections remain a major determinant of adverse outcomes in this population despite advances in antimicrobial therapy and critical care support (2).

Beyond direct pathogen-mediated injury, dysregulated pulmonary and systemic inflammatory responses contribute to respiratory failure, multiorgan dysfunction, and death, providing a biological rationale for adjunctive immunomodulatory therapy (3).

Recent randomized trials have renewed interest in adjunctive corticosteroid therapy for severe community-acquired pneumonia (CAP). Earlier trials reported inconsistent effects on mortality (4); however, the CAPE COD trial demonstrated that early hydrocortisone administration reduced 28-day mortality, the need for endotracheal intubation, and vasopressor-dependent shock in critically ill patients with severe CAP (5). Subsequent meta-analyses have generally confirmed improvements in mortality and other clinically relevant outcomes, although the magnitude of benefit appears to depend on disease severity and the corticosteroid regimen used (6).

Whether these findings can be extrapolated to critically ill patients with cancer remains uncertain. Patients with malignancy have been consistently underrepresented in randomized clinical trials conducted in the intensive care unit, particularly in studies evaluating mortality, thereby limiting the external validity of available evidence for oncologic populations (7). Accordingly, the major randomized trials evaluating adjunctive corticosteroids for severe community-acquired pneumonia either excluded patients with clinically important immunosuppression, as in CAPE COD (5), or included very few patients with active malignancy, as in ESCAPe (4). Cancer patients also constitute a highly heterogeneous group, with immune competence varying according to tumor type, disease stage, prior antineoplastic therapy, and hematopoietic stem-cell transplantation (1, 2). These factors influence both the host inflammatory response and the spectrum of causative pathogens, producing clinical phenotypes that differ substantially from those of immunocompetent patients (2). Corticosteroids are also frequently administered in oncology practice for indications unrelated to pneumonia - including treatment-related toxicities, cerebral edema, antiemetic regimens, graft-versus-host disease, and as components of chemotherapy for hematologic malignancies - which may alter baseline immune status and modify the response to corticosteroid therapy during critical illness (2). The efficacy and safety of adjunctive corticosteroids in patients with cancer may therefore differ from those observed in the general critically ill population.

In the absence of randomized trials specifically addressing critically ill patients with cancer, observational studies designed according to the target trial framework offer an opportunity to estimate treatment effects while minimizing biases inherent to conventional observational analyses (8). We therefore emulated a target trial using the Medical Information Mart for Intensive Care IV (MIMIC-IV) database to estimate the effect of early systemic corticosteroid administration on hospital mortality among critically ill adults with active malignancy and nonviral pneumonia.

METHODS

Study Design and Data Source

We conducted a target trial emulation using the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1), a publicly available, de-identified critical care database containing detailed information on patients admitted to the intensive care units of Beth Israel Deaconess Medical Center between 2008 and 2022. The study was designed according to the target trial framework proposed by Hernán and Robins (8) to emulate the protocol of a hypothetical randomized clinical trial evaluating early corticosteroid initiation in critically ill patients with cancer and nonviral pneumonia (Supplementary Table S1 and S2).

Eligibility Criteria

Eligible patients were adults admitted to the ICU with active malignancy and pneumonia.

Active malignancy was identified using ICD-9-CM and ICD-10-CM diagnosis codes corresponding to invasive solid, metastatic, and hematologic malignancies recorded during the index hospitalization. The complete list of diagnostic code ranges is provided in Supplementary Table S3.

Patients with viral pneumonia were excluded because corticosteroid indications, pathophysiology, and clinical outcomes differ substantially from those of bacterial and other nonviral pneumonias.

To emulate treatment assignment while minimizing immortal time bias, we adopted a 48-hour grace period followed by a landmark analysis. Patients who died or were discharged within the first 48 hours after ICU admission were excluded because they could not complete the treatment assignment window. Consequently, follow-up began at the 48-hour landmark among patients who remained alive and hospitalized.

Treatment Strategies and Exposure Assignment

The emulated target trial compared two treatment strategies: early initiation of systemic corticosteroids within the first 48 hours after ICU admission versus no systemic corticosteroid administration during the same period. ICU admission was defined as time zero, and the first 48 hours constituted the grace period during which treatment strategy was ascertained. Patients who remained alive and hospitalized at the end of the grace period were classified according to the treatment strategy initiated during this interval, consistent with an intention-to-treat approach. Follow-up for outcome assessment began at the 48-hour landmark.

Treatment assignment was determined using medication administration records available during the 48-hour grace period. Early corticosteroid initiation was defined as the administration of any systemic corticosteroid within this interval. No minimum cumulative dose, treatment duration, or hydrocortisone-equivalent threshold was required for treatment assignment. Corticosteroid exposure was identified by querying medication administration records using medication names, product strengths, and formulary

drug codes corresponding to hydrocortisone, methylprednisolone, dexamethasone, prednisone, prednisolone, and cortisone.

Outcomes

The primary outcome was hospital mortality, defined as death before hospital discharge. Secondary outcomes included intensive care unit (ICU) length of stay, hospital length of stay, and duration of invasive mechanical ventilation. ICU and hospital length of stay were calculated from administrative admission and discharge timestamps, whereas duration of invasive mechanical ventilation was derived from respiratory support records.

Covariates

Baseline covariates were prespecified based on biological plausibility and their potential association with both corticosteroid initiation and clinical outcomes. Covariates included demographic characteristics (age and sex), cancer-related variables (metastatic disease and hematologic malignancy), early organ support (vasopressor therapy, invasive mechanical ventilation, and noninvasive ventilation), physiological severity markers (arterial lactate, arterial oxygen tension [PaO_2], oxygen saturation [SpO_2], respiratory rate, mean arterial pressure, and Glasgow Coma Scale score), laboratory measurements (creatinine, bilirubin, platelet count, albumin, and white blood cell count), and clinically relevant comorbidities, including chronic obstructive pulmonary disease, asthma, adrenal insufficiency, brain metastasis or primary central nervous system tumor, cerebral edema, pneumonitis or interstitial lung disease, transplantation or immunosuppression, and autoimmune or rheumatologic disease. Laboratory variables were obtained during the first 24 hours after ICU admission.

Propensity Score Estimation

Propensity scores were estimated using multivariable logistic regression including 22 prespecified baseline covariates with adequate data availability. Albumin, bilirubin, lactate, and arterial oxygen tension (PaO_2), although considered a priori as potentially relevant covariates, were excluded from the final specification of the primary propensity score model because of substantial missingness. Missing data for covariates retained in the propensity score model were handled using a complete-case approach, and no multiple imputation was performed. The extent of missingness across candidate baseline covariates is reported in Supplementary Table S5. Inverse probability of treatment weighting (IPTW) with stabilized weights was used to generate a weighted pseudo-population. Stabilized weights were truncated at the 1st and 99th percentiles to reduce the influence of extreme observations. Covariate balance before and after weighting was assessed using absolute standardized mean differences (SMDs), with values < 0.10 considered indicative of adequate balance. The positivity assumption was evaluated by visual inspection of propensity score distributions to confirm adequate overlap between treatment groups.

Primary Analysis

The primary analysis estimated the effect of the early corticosteroid initiation strategy on hospital mortality using IPTW-weighted generalized linear models with a binomial distribution and robust standard errors. Treatment effects were reported as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Secondary continuous outcomes were analyzed using IPTW-weighted generalized linear models with a gamma distribution and log link, with treatment effects reported as ratios of means with 95% CIs.

Sensitivity Analyses

Two prespecified sensitivity analyses were performed to evaluate the robustness of the primary findings. First, treatment exposure was redefined as initiation of systemic corticosteroids within the first 24 hours after ICU admission. Second, propensity score matching was performed using 1:1 nearest-neighbor matching without replacement. As an additional robustness analysis, a conventional multivariable logistic regression model was fitted including the same 22 baseline covariates used in the primary propensity score model. Missing covariate data were handled using the same complete-case approach as in the primary analysis. Covariate balance in the matched cohort was assessed using absolute standardized mean differences.

Subgroup Analyses

Prespecified subgroup analyses were conducted according to invasive mechanical ventilation within the first 48 hours after ICU admission, vasopressor use within the first 48 hours after ICU admission, hematologic malignancy, and metastatic disease. Effect modification was evaluated by fitting separate IPTW-weighted logistic regression models including a multiplicative interaction term between treatment assignment and each subgroup variable. Two-sided p values for interaction were estimated for each prespecified subgroup analysis.

Exploratory Neutropenia Analysis

An exploratory analysis was performed among patients with available absolute neutrophil count (ANC) measurements obtained within the first 24 hours after ICU admission. ANC values were obtained from directly measured results when available or reconstructed from contemporaneous white blood cell counts and neutrophil differentials. Neutropenia was defined using thresholds of $< 1.5 \times 10^3/\mu L$, $< 1.0 \times 10^3/\mu L$, and $< 0.5 \times 10^3/\mu L$. Additional models evaluated the association between neutropenia and hospital mortality and explored potential effect modification by early corticosteroid initiation.

Statistical Analysis

All statistical analyses were performed using Python version 3.12.13. The principal libraries included pandas (2.2.2), NumPy (2.0.2), SciPy (1.16.3), statsmodels (0.14.6), scikit-learn (1.6.1), and Matplotlib

(3.10.0). All statistical tests were two-sided, and p values < 0.05 were considered statistically significant. Results from exploratory analyses were interpreted as hypothesis-generating. No formal sample size calculation was performed; the study sample comprised all eligible patients available in MIMIC-IV during the study period.

RESULTS

Study Population

Baseline characteristics of the analytic cohort are presented in Table 1. A total of 2,227 patients met the eligibility criteria and remained alive and hospitalized through the 48-hour landmark, constituting the primary landmark cohort. Within the treatment assignment window, 531 patients (23.8%) initiated systemic corticosteroids, whereas 1,696 (76.2%) did not. After exclusion of 67 patients (3.0%) because of missing covariate data required for propensity score estimation, the complete-case analytic cohort comprised 2,160 patients, including 521 assigned to the early corticosteroid initiation strategy and 1,639 assigned to the no-corticosteroid strategy. (Fig. 1).

Table 1
Baseline Characteristics and Covariate Balance Before and After Inverse Probability of Treatment Weighting (IPTW)

Variable	Before IPTW			After IPTW		
	Control	Steroid	SMD	Control	Steroid	SMD
Age, years	67.37 ± 13.42	64.17 ± 13.27	0.24	66.63 ± 13.51	66.29 ± 12.74	0.03
Female sex	39.5%	38.0%	0.03	39.4%	40.2%	0.02
Metastatic disease	40.1%	40.5%	0.01	40.4%	40.5%	0.00
Hematologic malignancy	21.5%	30.3%	0.20	23.0%	22.7%	0.01
Vasopressor use within 48h	32.0%	32.2%	0.01	31.9%	33.5%	0.04
Invasive ventilation within 48h	30.5%	34.0%	0.07	31.5%	33.9%	0.05
Noninvasive ventilation within 48h	4.3%	7.1%	0.12	5.0%	5.1%	0.00
Lowest SpO_2 within 24 h	90.54 ± 5.16	90.30 ± 5.18	0.05	90.49 ± 5.20	90.36 ± 5.05	0.02
Maximum RR within 24h	31.07 ± 6.79	30.94 ± 6.94	0.02	31.06 ± 6.80	31.12 ± 7.19	0.01
Lowest MAP within 24h	58.88 ± 11.76	60.21 ± 11.74	0.11	59.23 ± 11.84	59.19 ± 11.61	0.00
Lowest GCS within 24h	11.42 ± 4.28	11.14 ± 4.62	0.06	11.35 ± 4.32	11.22 ± 4.61	0.03
Peak SCr within 24h, mg/dL	1.46 ± 1.84	1.31 ± 1.92	0.08	1.43 ± 1.78	1.46 ± 2.43	0.01
Lowest platelet count within 24h	231.51 ± 56.77	202.60 ± 134.71	0.19	225.34 ± 153.85	222.70 ± 146.57	0.02

Values are presented as mean ± SD for continuous variables and percentages for categorical variables. Absolute standardized mean differences (SMDs) are shown before and after inverse probability of treatment weighting (IPTW).

The primary propensity score model included 22 prespecified baseline covariates with adequate data availability. Albumin, bilirubin, lactate, and PaO_2 were excluded from the final propensity score specification because of substantial missingness. Missing data for covariates retained in the model were handled using complete-case analysis.

Abbreviations: IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; SD, standard deviation; RR, respiratory rate; MAP, mean arterial pressure; GCS, Glasgow Coma Scale; SCr, serum creatinine; WBC, white blood cell count; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; ILD, interstitial lung disease.

Variable	Before IPTW			After IPTW		
	Control	Steroid	SMD	Control	Steroid	SMD
Maximum WBC within 24h	18.50 ± 27.88	16.02 ± 19.86	0.10	18.03 ± 26.75	18.52 ± 25.37	0.02
COPD	27.0%	39.5%	0.26	30.4%	32.7%	0.05
Asthma	5.4%	8.3%	0.11	6.1%	6.4%	0.02
Adrenal insufficiency	0.5%	5.8%	0.30	1.1%	2.0%	0.07
Brain metastasis/CNS tumor	23.0%	33.2%	0.23	25.7%	27.2%	0.03
Cerebral edema	2.3%	6.1%	0.19	3.2%	3.3%	0.00
Pneumonitis/ILD	10.9%	13.6%	0.08	11.4%	11.7%	0.01
Transplant /immunosuppression	7.6%	12.5%	0.16	8.9%	9.4%	0.02
Rheumatologic disease	3.1%	5.6%	0.12	3.9%	4.4%	0.02

Values are presented as mean ± SD for continuous variables and percentages for categorical variables. Absolute standardized mean differences (SMDs) are shown before and after inverse probability of treatment weighting (IPTW).

The primary propensity score model included 22 prespecified baseline covariates with adequate data availability. Albumin, bilirubin, lactate, and PaO_2 were excluded from the final propensity score specification because of substantial missingness. Missing data for covariates retained in the model were handled using complete-case analysis.

Abbreviations: IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; SD, standard deviation; RR, respiratory rate; MAP, mean arterial pressure; GCS, Glasgow Coma Scale; SCr, serum creatinine; WBC, white blood cell count; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; ILD, interstitial lung disease.

Propensity Score Performance

Before weighting, baseline covariate imbalance was observed between treatment groups, with a maximum absolute standardized mean difference (SMD) of 0.306. After inverse probability of treatment weighting (IPTW), adequate balance was achieved across all covariates included in the primary propensity score model, reducing the maximum absolute SMD to 0.069, with no covariate exceeding the prespecified threshold of 0.10 (Fig. 2). Baseline characteristics before and after weighting are summarized in Table 1, and detailed covariate balance is presented in Supplementary Table S4. IPTW reduced the number of covariates with an absolute SMD > 0.10 from 13 before weighting to none after weighting.

Primary Outcome

In the primary IPTW analysis, early initiation of systemic corticosteroids was not associated with hospital mortality (OR, 1.01; 95% CI, 0.80–1.27; p = 0.925). The multivariable-adjusted model yielded virtually identical estimates (OR, 1.00; 95% CI, 0.78–1.28; p = 0.993), supporting the robustness of the primary findings. Results were consistent across the prespecified sensitivity analyses (Fig. 3 and Table 2).

Table 2
Primary and Secondary Outcomes According to Early Corticosteroid Initiation

Outcome	Analysis	Effect measure	Estimate (95%CI)	P value
Hospital mortality	Primary analysis	OR	**1.01 (0.80–1.27)**	0.925
Hospital mortality	24-h exposure window	OR	**1.02 (0.80–1.30)**	0.869
Hospital mortality	Propensity score matching	OR	**1.17 (0.88–1.55)**	0.281
Hospital length of stay	Primary analysis	Ratio of means	**0.78 (0.71–0.85)**	< 0.001
ICU length of stay	Primary analysis	Ratio of means	**1.04 (0.92–1.17)**	0.550
Duration of invasive mechanical ventilation	Primary analysis	Ratio of means	**1.17 (0.95–1.44)**	0.132

The primary analysis used IPTW-weighted generalized linear models. Odds ratios (ORs) are reported for hospital mortality. Continuous outcomes were analyzed using IPTW-weighted gamma regression models with a log link and are presented as ratios of means.

Abbreviations: CI, confidence interval; ICU, intensive care unit; IPTW, inverse probability of treatment weighting; LOS, length of stay; OR, odds ratio.

Sensitivity Analyses

Sensitivity analyses yielded results consistent with the primary analysis. Redefining early corticosteroid initiation using a 24-hour exposure window did not materially alter the estimated association with hospital mortality (OR, 1.02; 95% CI, 0.80–1.30; P = 0.869). Similarly, propensity score matching yielded 521 matched pairs, with no significant association between early corticosteroid initiation and hospital mortality in the matched cohort (OR, 1.17; 95% CI, 0.88–1.55; P = 0.281). Overall, estimates remained consistent across alternative exposure definitions and propensity score approaches (Fig. 3).

Secondary Outcomes

Early corticosteroid initiation was associated with a shorter hospital length of stay (ratio, 0.78; 95% CI, 0.71–0.85; p < 0.001). No significant differences were observed in ICU length of stay (ratio, 1.04; 95% CI,

0.92–1.17; p = 0.550) or duration of invasive mechanical ventilation (ratio, 1.17; 95% CI, 0.95–1.44; p = 0.132) (Table 2).

Subgroup Analyses

In prespecified subgroup analyses, no evidence of effect modification was observed according to invasive mechanical ventilation (P for interaction = 0.135), hematologic malignancy (P for interaction = 0.654), or metastatic disease (P for interaction = 0.677). In contrast, a statistically significant interaction was observed according to vasopressor use (P for interaction = 0.024), suggesting that the association between early corticosteroid initiation and hospital mortality differed according to baseline shock status (Fig. 3).

Exploratory Neutropenia Analysis

Absolute neutrophil count (ANC) measurements were available for 1,003 patients (46.4% of the analytic cohort), including directly measured values and reconstructed counts derived from contemporaneous white blood cell counts and neutrophil differentials. Neutropenia was identified in 141 patients using an ANC threshold of < 1.5 ×10³/μL, 119 patients using < 1.0 ×10³/μL, and 86 patients using < 0.5 ×10³/μL. In exploratory analyses, ANC < 1.0 ×10³/μL was independently associated with higher hospital mortality (OR, 1.64; 95% CI, 1.02–2.64; p = 0.041). Although hospital mortality increased with increasing neutropenia severity, no statistically significant interaction was observed between neutropenia and early corticosteroid initiation across any ANC threshold.

DISCUSSION

In this target trial emulation of critically ill patients with active malignancy and nonviral pneumonia, early initiation of systemic corticosteroids was not associated with hospital mortality. The effect estimate was centered near the null and remained consistent across inverse probability of treatment weighting, conventional multivariable adjustment, an alternative 24-hour treatment-assignment window, and propensity score matching. No evidence of effect modification was observed according to invasive mechanical ventilation, metastatic disease, or hematologic malignancy. However, a statistically significant interaction was identified according to vasopressor use, suggesting that the association between early corticosteroid initiation and hospital mortality may differ according to baseline shock status.

Our findings differ from those of several contemporary studies of severe community-acquired pneumonia conducted predominantly in immunocompetent populations. In the CAPE COD trial, early hydrocortisone reduced 28-day mortality and the subsequent need for endotracheal intubation or vasopressor therapy among patients admitted to the ICU with severe community-acquired pneumonia (5). Subsequent meta-analyses have generally supported a mortality benefit from corticosteroids in severe community-acquired pneumonia, although treatment effects have varied according to disease severity, corticosteroid regimen, and the trials included (6, 9). Earlier randomized evidence was less consistent; the ESCAPe trial did not demonstrate a statistically significant mortality benefit with

prolonged low-dose methylprednisolone (4). More recently, the REMAP-CAP corticosteroid domain concluded that a large mortality reduction with a 7-day course of hydrocortisone was unlikely, although smaller benefits and potential harm could not be excluded (10). Collectively, these data indicate that the effects of corticosteroids in severe pneumonia are not uniform across populations, clinical contexts, and treatment protocols (11).

The present findings should therefore not be interpreted as directly contradicting CAPE COD. Rather, they address a different clinical population and a broader pneumonia phenotype. Trials of corticosteroids in community-acquired pneumonia have generally enrolled carefully selected patients and have excluded or underrepresented individuals with substantial immunosuppression, active malignancy, recent anticancer therapy, or opportunistic pulmonary infection. Patients with cancer differ from immunocompetent trial populations in the causes and severity of immune dysfunction, the spectrum of pulmonary pathogens, the prevalence of mixed infectious and noninfectious lung injury, and the competing indications for corticosteroid treatment (1, 2). These differences limit direct extrapolation of treatment effects from conventional severe community-acquired pneumonia trials.

The biological effects of corticosteroids may also differ in patients with cancer. In severe pneumonia, corticosteroids may attenuate an excessive inflammatory response responsible for alveolar and endothelial injury, impaired gas exchange, and organ dysfunction (3). In patients with malignancy, however, this potential benefit must be considered against baseline immune dysfunction related to the cancer itself, cytotoxic chemotherapy, hematopoietic stem-cell transplantation, immunomodulatory therapies, malnutrition, and prior or concurrent corticosteroid exposure. Additional immunosuppression may impair pathogen clearance or increase susceptibility to secondary and opportunistic infections, particularly when pneumonia is caused by fungi, Pneumocystis jirovecii, or other organisms uncommon in immunocompetent hosts (2, 12). The recent PIC trial further illustrates that findings from bacterial community-acquired pneumonia cannot be assumed to apply to opportunistic infections in non-HIV immunocompromised patients, in whom the balance between inflammatory lung injury and impaired antimicrobial immunity may be fundamentally different (13).

The heterogeneity of cancer-related immune dysfunction may also have diluted a treatment effect confined to a narrower phenotype. Patients with solid tumors, hematologic malignancies, metastatic disease, recent chemotherapy, transplantation, or treatment-related pneumonitis may have substantially different inflammatory and infectious profiles. Corticosteroids are also frequently administered in oncology for cerebral edema, antiemesis, hematologic malignancies, graft-versus-host disease, immune-related adverse events, and other treatment complications. Prior or concurrent exposure could alter baseline immune function, produce pharmacological tolerance, or result in treatment misclassification when corticosteroids administered for a nonpneumonia indication are classified as part of the early treatment strategy. Although the propensity score incorporated several clinically relevant indications for corticosteroid use, residual confounding by indication remains plausible.

Most prespecified subgroup analyses showed no evidence of effect modification. However, a statistically significant interaction was observed according to vasopressor use, suggesting potential heterogeneity of treatment effect according to baseline shock status. This finding should be interpreted cautiously. Interaction analyses generally have substantially lower statistical power than analyses of the overall treatment effect, and multiple subgroup comparisons increase the likelihood of chance findings. Moreover, vasopressor use may reflect differences in illness severity, septic shock, or the clinical indications prompting corticosteroid administration, making residual confounding by indication difficult to exclude despite propensity score adjustment. Consequently, this observation should be considered hypothesis-generating and requires confirmation in independent cohorts or randomized studies.

Early corticosteroid initiation was associated with a shorter hospital stay, whereas ICU length of stay and duration of invasive mechanical ventilation were not significantly different. Corticosteroids have previously been associated with more rapid clinical stabilization and shorter hospitalization in some studies of community-acquired pneumonia (14). However, the present finding should be interpreted cautiously. Hospital length of stay is influenced by mortality, discharge practices, rehabilitation needs, treatment limitations, and nonclinical factors, and death may act as a competing event for hospital discharge. The absence of corresponding reductions in ICU stay or mechanical ventilation duration also weakens a straightforward interpretation of shorter hospitalization as evidence of accelerated pulmonary recovery. Accordingly, this secondary result should be considered hypothesis-generating rather than evidence of an established resource-use benefit.

The exploratory neutropenia analysis provides additional information regarding the immunological heterogeneity of the cohort. Increasing neutropenia severity was associated with higher hospital mortality, although absolute neutrophil count was available in fewer than half of the analytic population. Previous evidence suggests that neutropenia is associated with illness severity and adverse outcomes among critically ill patients with cancer, but that its independent prognostic contribution may be attenuated after accounting for organ dysfunction and other determinants of acute severity (15). In our analysis, neutropenia did not detectably modify the association between early corticosteroid initiation and hospital mortality. This finding should be interpreted cautiously because the number of neutropenic patients was limited, interaction analyses were underpowered, and absolute neutrophil count alone does not fully characterize the depth, duration, or cause of immunosuppression. The results nevertheless support further evaluation of immune phenotypes rather than reliance on cancer diagnosis alone as a marker of treatment response.

This study has several strengths. The analysis was explicitly structured around a prespecified target trial, with alignment of eligibility assessment, time zero, treatment assignment, the 48-hour grace period, and the start of follow-up. This approach was intended to reduce immortal time bias and other design-related biases that can arise when treatment classification and follow-up are not temporally aligned. Treatment groups were balanced using stabilized inverse probability weights, with all measured covariates achieving the prespecified standardized mean difference threshold after weighting. Findings remained consistent across complementary adjustment strategies and alternative exposure windows. The study

was also reported according to the principles of transparent target trial emulation, including explicit description of the hypothetical trial protocol and its observational implementation (16).

Several limitations should be acknowledged. As in any observational study, residual confounding cannot be excluded despite extensive covariate adjustment, particularly because corticosteroids may have been prescribed for indications other than pneumonia, including septic shock, adrenal insufficiency, cerebral edema, obstructive airway disease, treatment-related pneumonitis, or other oncologic conditions. In addition, treatment was defined as any systemic corticosteroid administration during the assignment window, precluding evaluation of differences in agent, dose, duration, cumulative exposure, or treatment indication. Cancer and pneumonia were identified using diagnostic codes, and the database lacked detailed information on cancer stage, recent anticancer therapy, timing of hematopoietic stem-cell transplantation, performance status, prior outpatient corticosteroid use, and microbiological etiology, all of which may have influenced treatment selection and prognosis. The complete-case propensity score analysis and the 48-hour landmark design may also have introduced selection bias by restricting the analysis to patients with complete covariate data who survived and remained hospitalized through the treatment-assignment window, although the latter was necessary to minimize immortal time bias. Finally, this single-center study may have limited generalizability to other oncology populations, and the subgroup and neutropenia analyses should be interpreted as exploratory because they may have been underpowered to detect clinically important effect modification.

These findings do not support automatic extrapolation of the mortality benefit observed in selected trials of severe community-acquired pneumonia to critically ill patients with active malignancy and nonviral pneumonia. The observed interaction according to vasopressor use further suggests that treatment effects may differ across clinical phenotypes of critical illness and reinforces the need for phenotype-specific evaluation in future studies. At the same time, they should not be interpreted as evidence that adjunctive corticosteroids are ineffective or harmful in this population, as the confidence intervals remain compatible with both moderate benefit and moderate harm. Accordingly, our findings should be interpreted within the assumptions required for causal inference from observational data and should be confirmed in prospective studies whenever feasible. Future investigations should prioritize biologically and clinically homogeneous cancer populations, incorporate detailed characterization of immune status, recent anticancer therapies, infectious etiologies, and corticosteroid regimens, and evaluate biomarkers of host inflammatory and immune responses capable of identifying patients most likely to benefit from adjunctive corticosteroid therapy. In selected high-risk populations, randomized clinical trials remain the preferred source of evidence, whereas carefully designed multicenter target trial emulations may provide complementary evidence when randomized studies are not feasible.

CONCLUSION

Among critically ill adults with active malignancy and nonviral pneumonia who survived and remained hospitalized through a 48-hour treatment-assignment period, early systemic corticosteroid initiation was not associated with hospital mortality. The estimate remained stable across multiple analytical

approaches and prespecified clinical subgroups. These findings suggest that the benefits observed in selected populations with severe community-acquired pneumonia should not be assumed to extend uniformly to critically ill patients with cancer and support further phenotype-specific evaluation of corticosteroid therapy.

ABREVIATIONS

ANC – Absolute Neutrophil Count

CAP – Community-Acquired Pneumonia

CI – Confidence Interval

CNS – Central Nervous System

COPD – Chronic Obstructive Pulmonary Disease

GCS – Glasgow Coma Scale

ICD – International Classification of Diseases

ICD-9-CM – International Classification of Diseases, Ninth Revision, Clinical Modification

ICD-10-CM – International Classification of Diseases, Tenth Revision, Clinical Modification

ICU – Intensive Care Unit

ILD – Interstitial Lung Disease

IPTW – Inverse Probability of Treatment Weighting

MAP – Mean Arterial Pressure

MIMIC-IV – Medical Information Mart for Intensive Care IV

OR – Odds Ratio

PaO_2 – Arterial Partial Pressure of Oxygen

RR – Respiratory Rate

SCr – Serum Creatinine

SD – Standard Deviation

SMD – Standardized Mean Difference

SpO_2 – Peripheral Oxygen Saturation

WBC – White Blood Cell Count

DECLARATIONS

Data Availability Statement

The data used in this study were obtained from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1) database. MIMIC-IV is a publicly available, de-identified clinical database accessible through PhysioNet to credentialed users who complete the required training and agree to the applicable data use agreement. The authors are not permitted to redistribute the underlying patient-level data. The data can be accessed directly through PhysioNet following completion of the required credentialing procedures.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

The collection of patient information and creation of the MIMIC-IV research resource were reviewed by the Institutional Review Board of Beth Israel Deaconess Medical Center, which approved the data-sharing initiative and granted a waiver of informed consent. The present study was a secondary analysis of de-identified MIMIC-IV data accessed by credentialed investigators in accordance with the PhysioNet Data Use Agreement.

Consent to participate

The requirement for individual informed consent was waived because this study used de-identified data from the MIMIC-IV database. The investigators had no direct contact with study participants and had access only to de-identified patient data.

Consent for publication

Not applicable. This study used only de-identified data from the MIMIC-IV database and contains no identifiable individual participant information.

Generative AI Disclosure

During the preparation of this work the author(s) used ChatGPT-5 in order to assist with English language refinement and correction of minor editorial errors after the manuscript was completed. After using this tool, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Author Contribution

All authors contributed to the study conception and design. Material preparation and data collection were perfomed by L.G.P., MGC, M.F.F.a and A.P.V.F. Analysis were performed by R.H.M. The first draft of the manuscript was written by L.G.P. and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

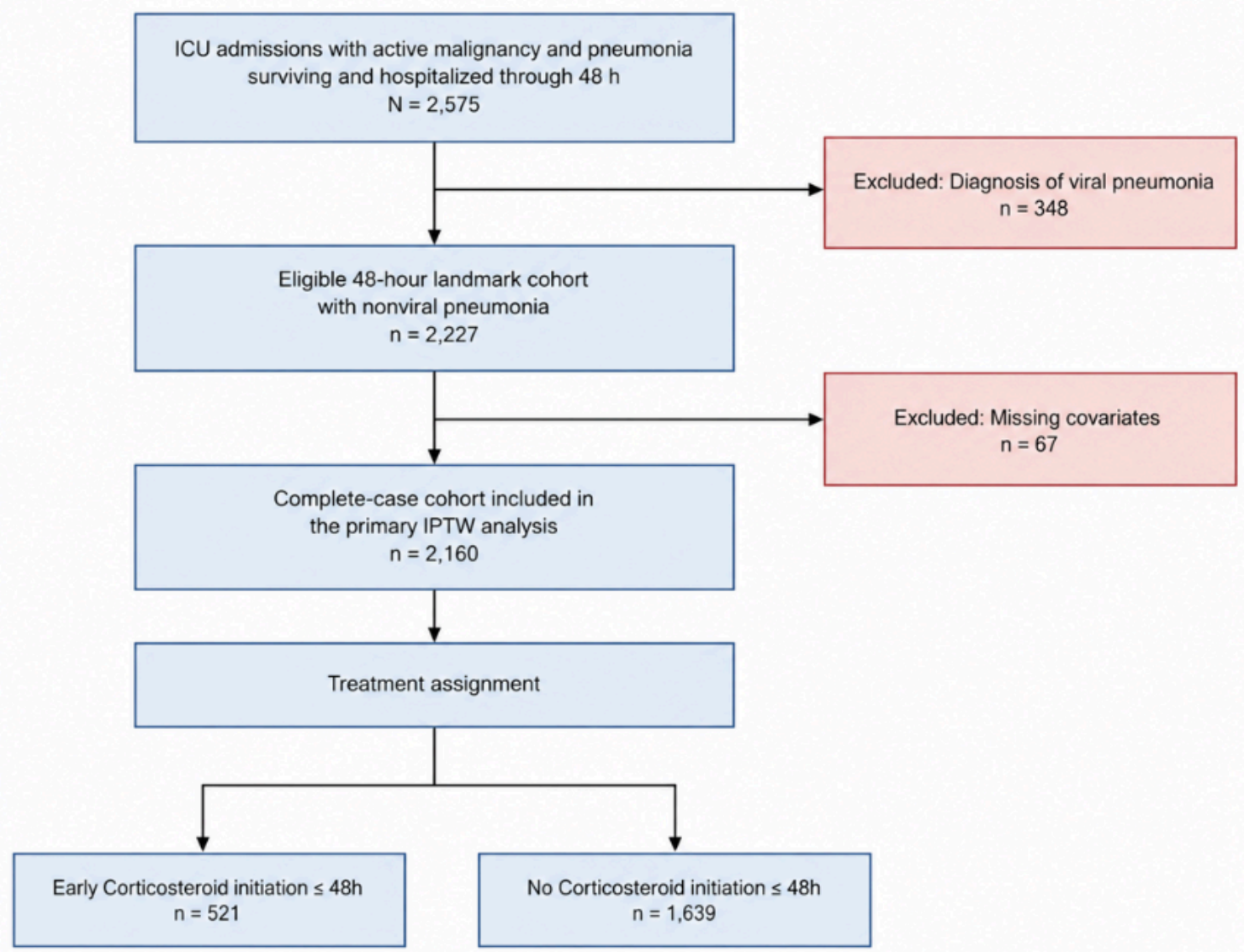


Figure 1

Target Trial Emulation Study Flow

Follow-up began at the 48-hour landmark and continued until hospital discharge or in-hospital death.

Patients remained alive and hospitalized throughout the 48-hour treatment-assignment period (landmark). Patients with missing baseline covariate data required for propensity score estimation were excluded from the complete-case primary analysis.

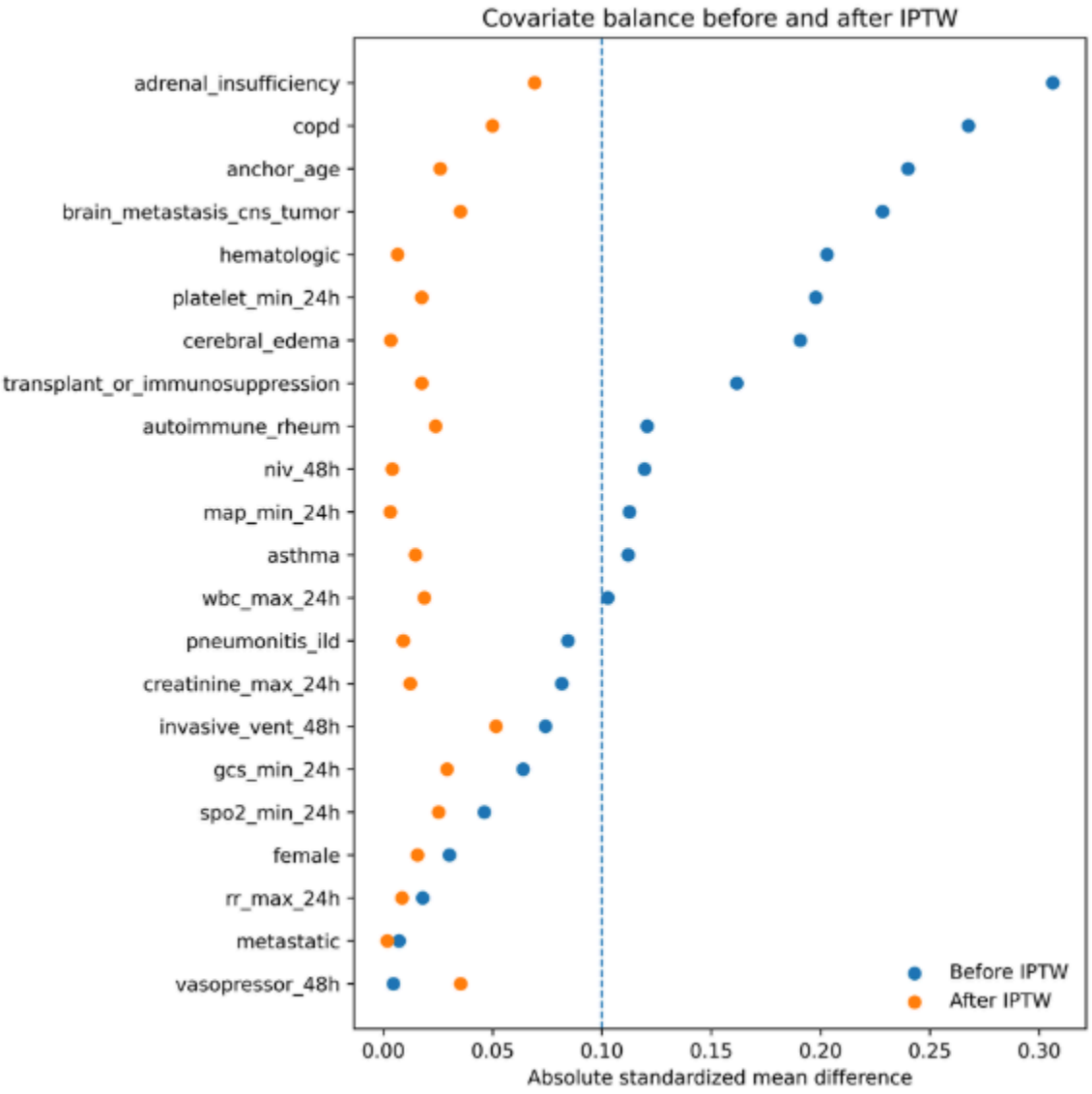


Figure 2

Covariate Balance Before and After Inverse Probability of Treatment Weighting (IPTW)

Legend: Absolute standardized mean differences (SMDs) for the 22 baseline covariates included in the final primary propensity score model before and after inverse probability of treatment weighting (IPTW). The dashed vertical line indicates the prespecified threshold for adequate covariate balance (absolute SMD <0.10).

Abbreviations: CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; IPTW, inverse probability of treatment weighting; MAP, mean arterial pressure; SMD, standardized mean difference; SpO_2, peripheral oxygen saturation.

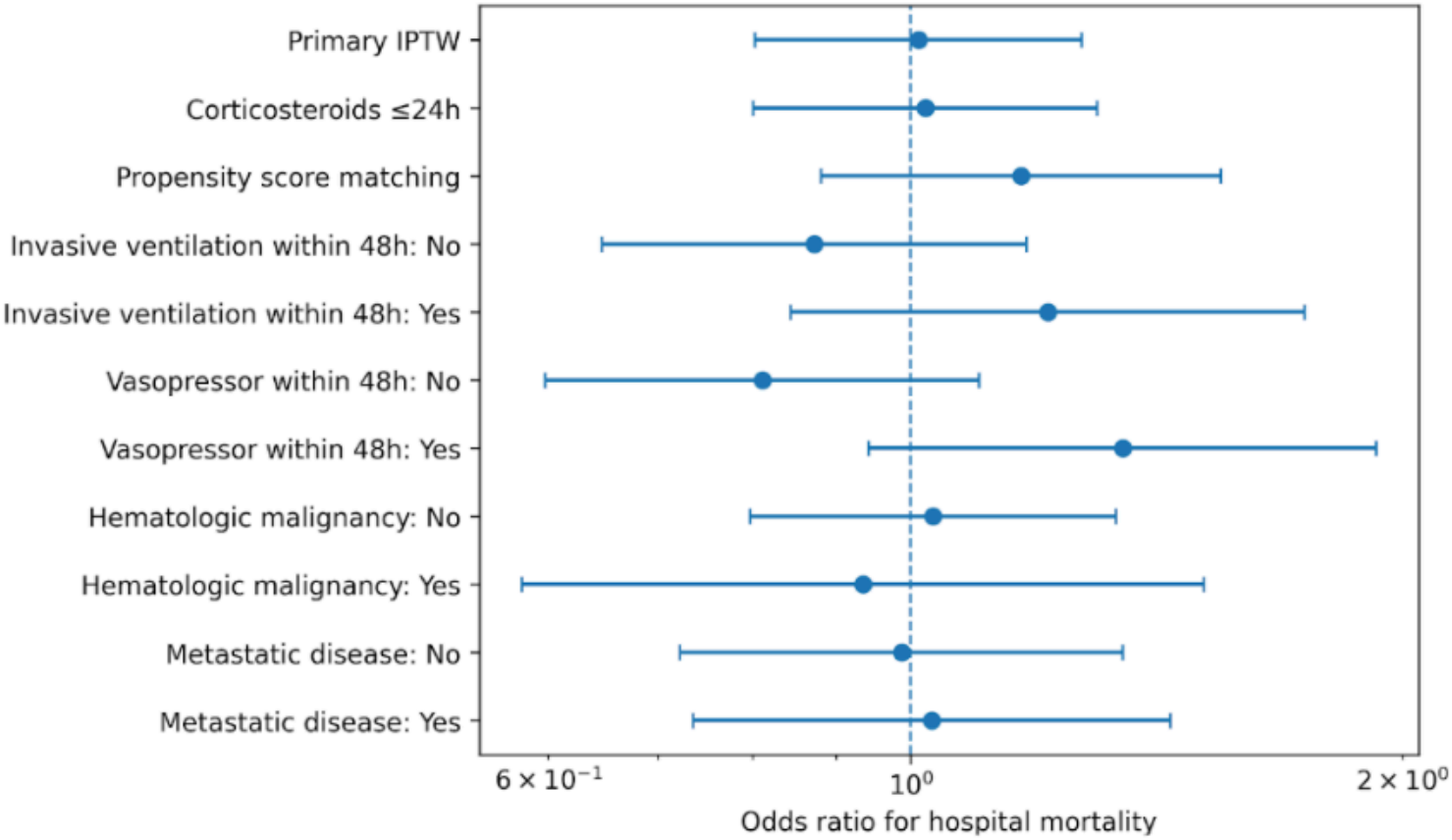


Figure 3

Association Between Early Corticosteroid Initiation and Hospital Mortality Across Primary, Sensitivity, and Subgroup Analyses

Legend: Odds ratios (ORs) and 95% confidence intervals (CIs) for the association between early corticosteroid initiation and hospital mortality across the primary analysis, prespecified sensitivity analyses, and prespecified subgroup analyses. The vertical dashed line represents the null effect (OR = 1.0). Subgroup estimates were obtained from IPTW-weighted models, and effect modification was evaluated using multiplicative interaction terms.

Abbreviations: CI, confidence interval; IPTW, inverse probability of treatment weighting; OR, odds ratio.

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