HHS Public Access

Author manuscript

*Crit Care Med*. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

*Crit Care Med*. 2017 December ; 45(12): 2055–2060. doi:10.1097/CCM.0000000000002763.

# Outcomes of Intensive Care Unit Patients with a Discharge Diagnosis of Critical Illness Polyneuromyopathy: A Propensity Matched Analysis

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## Abstract

**Objectives—**To assess the impact of a discharge diagnosis of critical illness polyneuromyopathy on health-related outcomes in a large cohort of patients requiring intensive care unit (ICU) admission.

**Design—**Retrospective cohort with propensity score matched analysis.

**Setting—**Analysis of a large multi-hospital database.

**Patients—**Adult ICU patients without pre-existing neuromuscular abnormalities and a discharge diagnosis of critical illness polyneuropathy and/or myopathy (CIPNM) along with adult ICU propensity matched control patients.

**Interventions—**None.

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**Work performed at:** University of Colorado School of Medicine

**Conflicts of interest:** None declared

**Copyright form disclosure:** Drs. Kelmenson, Quan, Burnham, and Moss received support for article research from the National Institutes of Health (NIH). Dr. Quan's institution received funding from the NIH, Pfizer, and Alnylam (clinical research), and she received funding from Alnylam (speaker payment), Cytokinetics, WebMD (royalties), and UptoDate (royalties). Dr. Kiser's institution received funding from Allergan and Astellas. Dr. Moss' institution received funding from NIH/National Heart, Lung, and Blood Institute. The remaining authors have disclosed that they do not have any potential conflicts of interest.

**Measurements and Main Results—**Of 3,567 ICU patients with a discharge diagnosis of CIPNM, we matched 3,436 of these patients to 3,436 ICU patients who did not have a discharge diagnosis of CIPNM. After propensity matching and adjusting for unbalanced covariates, we used conditional logistic regression and a repeated measures model to compare patient outcomes. Compared to patients without a discharge diagnosis of CIPNM, patients with a discharge diagnosis of CIPNM had fewer 28-day hospital free days (6 [0.1] vs 7.4 [0.1] days, p<0.0001), fewer 28-day ventilator free days (15.7 [0.2] vs 17.5 [0.2] days, p<0.0001), higher hospitalization charges (313,508 [4,853] vs 256,288 [4,470] dollars, p<0.0001), were less likely to be discharged home (15.3% vs 32.8%, p<0.0001), but had lower in-hospital mortality (13.7% vs 18.3%, p<0.0001).

**Conclusions—**In a propensity matched analysis of a large national database, a discharge diagnosis of CIPNM is strongly associated with deleterious outcomes including fewer hospital free days, fewer ventilator free days, higher hospital charges, and reduced discharge home, but also an unexpectedly lower in-hospital mortality. This study demonstrates the clinical importance of a discharge diagnosis of CIPNM and the need for effective preventive interventions.

### Keywords

Critical Care; Critical Care Outcomes; Critical Illness; Muscle Weakness; Muscular Diseases; Polyneuropathies

## INTRODUCTION

Each year, more than 75,000 mechanically ventilated patients in the United States develop weakness as a result of their intensive care unit (ICU) stay, a condition termed ICU-acquired weakness (ICUAW) (1). This is likely an underestimation of the true prevalence of ICUAW, as many patients will develop weakness due to sepsis or multi-organ failure without undergoing mechanical ventilation (2–5). The incidence of weakness in critically ill patients varies by study, but ranges from 25% in patients on prolonged mechanical ventilation to 75% in patients with sepsis or multi-organ failure (6–15). Weakness may take the form of deconditioning (weakness without electrophysiologic abnormalities), but the majority of these critically ill patients have weakness with associated electrophysiologic abnormalities, known as critical illness polyneuropathy and/or myopathy (CIPNM) (6, 9, 10, 16, 17).

In small studies, ICUAW and CIPNM have been associated with deleterious outcomes including prolonged mechanical ventilation (6, 7, 16, 18, 19), longer ICU and hospital length of stay (LOS) (7, 18–20), higher hospital costs (18, 21), and increased hospital mortality (7, 10, 11, 17, 19). However, due to the small size of most of these studies, they were unable to adequately account for multiple potential confounding factors such as age, comorbidities, mechanical ventilation, vasopressor use, and ICU LOS (6, 10, 17–19). Of the two studies assessing hospital costs, one study only included 10 patients (18) and the other was a European study where hospital-related costs may be different (21). In addition, all the studies were performed at centers with unique expertise in acquired neuromuscular dysfunction resulting from critical illness. Therefore, it is currently unknown whether these results are generalizable on a national level. Additionally, none of these studies examined the effects of a diagnosis of CIPNM on hospital readmissions.

Therefore, we used a 5-year national database of ICU patients to define the epidemiology of CIPNM and determine if CIPNM is independently associated with a variety of deleterious outcomes. If CIPNM is associated with adverse patient outcomes, this information will help clinicians and families better characterize the prognosis of patients diagnosed with CIPNM and should spur increased efforts to find interventions to prevent, diagnose and treat CIPNM.

## MATERIALS AND METHODS

### Population and Inclusion/Exclusion Criteria

This was a multicenter observational cohort study using data from the Premier Healthcare Database. This fee-supported database contains patient-level data from over 700 hospitals throughout the United States. It contains the inpatient records from more than 80 million hospitalizations and over 6 million visits are added each year, representing 20% of national inpatient discharges. Included hospitals vary in size and geographic location but are predominantly <500 beds, non-teaching, and serve an urban patient population. The database contains hospital and patient characteristics, International Classification of Diseases-9 (ICD-9) and Current Procedural Terminology (CPT) codes, outcomes such as readmissions and mortality, and a date stamped log of all billed items including medications, labs, diagnostic and therapeutic procedures, and administration, which allows calculation of hospital charges. We obtained a subset of the entire database that includes only patients who spent part of their hospitalization in the ICU.

Our inclusion criteria were patients 18 years of age or older admitted to the ICU from 2010–2014 who during their hospitalization received an ICD-9 diagnosis code for critical illness polyneuropathy (357.82) and/or critical illness myopathy (359.81). We excluded patients transferred to/from another acute care hospital (but included long-term acute care facilities [LTACs]) as a lack of patient-level data for hospitals not participating in the Premier Healthcare Database would not permit accurate outcome measurement. We excluded patients with an ICD-9 code indicating another pre-existing or acquired neuromuscular abnormality besides CIPNM. We also excluded patients with an ICD-9 code for CIPNM already present on admission, in order to examine patients who developed CIPNM during their hospitalization rather than patients who had CIPNM as a pre-existing condition (presumably from a prior hospitalization). Although the ICD-9 codes for CIPNM were recorded at the time of discharge, CIPNM presumably developed during the hospitalization (and not just at the time of discharge) since we excluded patients who had CIPNM coded at the time of admission. The Colorado Multiple Institutional Review Board (IRB) approved the study with a waiver of informed consent since the data was aggregated and de-identified. Some of this data was previously presented as an abstract at the American Thoracic Society International Conference 2017.

### ICD-9 Validation

Given an absence of studies that used these ICD codes to identify adult patients with CIPNM, we validated the specificity of our ICD-9 inclusion criteria. Data from a random sampling of 50 patients admitted to the University of Colorado Hospital from 2010–2014 with a primary or secondary discharge ICD-9 code of 357.82 and/or 359.81 were obtained.

We considered the code consistent with a diagnosis of CIPNM if the patient had no weakness or significant neuromuscular diagnosis on admission and then developed severe weakness (Medical Research Council muscle strength score <48) and/or had abnormal nerve conduction studies/electromyography (NCS/EMG) consistent with CIPNM per the reading neurologist during their hospitalization. This sub-study was also approved by our IRB.

## Propensity Matching

We chose to do propensity matching (in addition to regression) because it was robust to non-linear covariates, allowed us to balance our two matched groups on many covariates without having to exclude a large number of patients, and would effectively account for multiple covariates even if relatively few patients had some of the outcome events (such as readmission) (22). We performed 1:1 propensity score matching to compare ICU patients with a discharge diagnosis of CIPNM to ICU patients without a discharge diagnosis of CIPNM, matching on both pre-illness and acute-illness patient and hospital characteristics. We used a nonparsimonious regression model to produce a propensity score for CIPNM, using the following variables in the model available in the Premier database and considered relevant to CIPNM: Age, gender, race, pre-existing comorbidities, type of primary health insurance, ICU LOS, pre-ICU hospital LOS, source of hospital admission (home or a chronic care facility), invasive mechanical ventilation on hospital day 1, non-invasive mechanical ventilation on hospital day 1, intravenous vasopressors (phenylephrine, norepinephrine, epinephrine, vasopressin, or dopamine) on hospital day 1, admission to a MICU vs another ICU, year of admission, hospital bed count, urban vs rural hospital population, geographic region of country, and teaching hospital status. We included ICU LOS in the propensity matched model to try to correct for ICU-related survivor bias and to remove the impact of a prolonged ICU stay (regardless of development of CIPNM) on the outcome of hospital LOS (23, 24). For the propensity matched analysis, each patient with a discharge diagnosis of CIPNM was matched with a patient without a discharge diagnosis of CIPNM to the nearest fifth decimal point. After propensity matching, we adjusted for any remaining differences in potential confounding variables (unbalanced covariates) before final analysis.

## Outcome Measures

The principal analysis for interpretation of study outcomes was the propensity score matched analysis adjusted for unbalanced covariates. We compared patients with a discharge diagnosis of CIPNM to patients without a discharge diagnosis of CIPNM on the following primary outcomes: 28-day hospital free days, total hospitalization charges, and discharge location (home vs elsewhere). We also explored the following secondary outcomes: hospital length of stay, 28-day ventilator free days, in-hospital mortality and 30-day readmission rate.

## Statistical Analysis

The model used for analysis of the association between a discharge diagnosis of CIPNM and outcomes differed depending on the outcome variable and population being modeled (full or propensity matched). For binary outcome models (in-hospital mortality, discharge location, and 30-day readmission status), logistic regression was used for the full dataset and conditional logistic regression with strata as the case number was used for the matched

subset. For continuous outcome models (hospital length of stay, 28-day hospital free days, 28-day ventilator free days, and total hospitalization charges), a general linear model was used for the full dataset and a repeated measures model with the repeated subject as the case number was used for the matched subset. The case number was the same for patients with a discharge diagnosis of CIPNM and matched patients without a discharge diagnosis of CIPNM. We compared baseline characteristics between groups using t-tests for continuous variables, logistic regression for binary variables and chi-square tests for counts. Outcomes are presented as percentages and odds ratios for binary outcomes or means and differences for continuous outcomes. All analyses were performed using SAS version 9.4 (Cary, NC). A p-value less than 0.05 was considered statistically significant and all significance tests were two-sided. There was no adjustment performed for multiple comparisons.

## RESULTS

### Patient and Hospital Characteristics

There were 3,567 adult patients in the Premier database admitted to an ICU from 2010–2014 with a discharge diagnosis of CIPNM who did not meet our pre-defined exclusion criteria. There were 2,807,147 patients without a discharge diagnosis of CIPNM who were eligible for propensity matching (Supplemental Table 1). As expected, these groups had divergent baseline characteristics in nearly all measured categories before propensity matching. When compared to patients without a discharge diagnosis of CIPNM, patients with a discharge diagnosis of CIPNM were more likely on day 1 of their hospitalization to be on invasive mechanical ventilation (38.6% vs 14.9%, $p<0.0001$), non-invasive mechanical ventilation (16% vs 6.4%, $p<0.0001$) or vasopressors (32% vs 17.1%, $p<0.0001$). Patients with a discharge diagnosis of CIPNM were also more likely to have a diagnosis of acute renal failure (31.8% vs 15.7%, $p<0.0001$), severe sepsis (28.8% vs 6.5%, $p<0.0001$), septic shock (20.3% vs 4.2%, $p<0.0001$), or acute respiratory distress syndrome (ARDS) (14.9% vs 3.1%, $p<0.0001$). Only 4.3% of CIPNM patients were coded as having NCS/EMG during their hospitalization.

### Propensity Matching

We successfully propensity matched 3,436 (96.3%) of the 3,567 patients with a discharge diagnosis of CIPNM to 3,436 patients without a discharge diagnosis of CIPNM (Supplemental Table 2). After propensity matching there were no significant differences in any of the baseline covariates between the two groups except for minor differences in ICU LOS and pre-ICU hospital LOS, which required further statistical adjustment to achieve balance between the groups. In the propensity matched groups, the median age was 65 years, 50% were female, 38% received invasive mechanical ventilation on day 1, 15% received non-invasive mechanical ventilation on day 1, and 31% received IV vasopressors on day 1. Compared to patients without a discharge diagnosis of CIPNM, patients with a discharge diagnosis of CIPNM were more likely to have been seen by physical therapy (90.4% vs 71.9%, $p<0.0001$) and occupational therapy (62.9% vs 42.7%, $p<0.0001$) during the hospitalization and were also seen slightly more often by physical therapy (1.4 [1.3] vs 1.1 [1.2] total sessions, $p<0.0001$) and occupational therapy (0.8 [0.9] vs 0.6 [0.9] total sessions, $p<0.0001$).

### Outcomes

After propensity score matching and adjustment for unbalanced covariates, there were significant differences between patients with and without a discharge diagnosis of CIPNM in most measured outcomes (Table 1). Compared to patients without a discharge diagnosis of CIPNM, patients with a discharge diagnosis of CIPNM had longer hospital stays (29.6 [0.4] vs 23.8 [0.4] days, p<0.0001), fewer 28-day hospital free days (6 [0.1] vs 7.4 [0.1] days, p<0.0001), and fewer 28-day ventilator free days (15.7 [0.2] vs 17.5 [0.2] days, p<0.0001). Patients with a discharge diagnosis of CIPNM incurred higher hospitalization charges of on average $57,220 (313,508 [4,853] vs 256,288 [4,470] dollars, p<0.0001). Following the acute hospitalization, patients with a discharge diagnosis of CIPNM were less likely to be discharged home (15.3% vs 32.8%, p<0.0001) and there was a non-significant increased likelihood of readmission within 30 days (8.9% vs 7.9%, p=0.16). In the unmatched unadjusted model, patients with a discharge diagnosis of CIPNM initially demonstrated higher mortality (13.9% vs 6.4%, p<0.0001), but after propensity matching and covariate adjustment, patients with a discharge diagnosis of CIPNM had lower in-hospital mortality (13.7% vs 18.3%, p<0.0001). This mortality difference was not explained by increased discharge to hospice in the CIPNM group, as matched patients with a discharge diagnosis of CIPNM were less frequently discharged to inpatient/outpatient hospice (2.8% vs 5.2%, p<0.0001). In a post-hoc analysis, we added variables for whether patients received PT or OT to the propensity model. There was no change in the direction of any outcomes, but there was an attenuated mortality difference between the two propensity matched groups (13.8% vs 14.4%, p=0.04).

### Validation of ICD-9 Codes

In our separate cohort of 50 patients coded as having CIPNM, 10 of the 50 patients (20%) underwent NCS/EMG during their hospitalization, of which 9/10 (90%) were positive for CIPNM. We confirmed the discharge diagnosis of CIPNM was consistent based on either documented weakness and/or abnormal NCS/EMG in 46 of the 50 patients, yielding a positive predictive value of 92% (95% confidence interval, 82% to 97%) for the 357.82 and/or 359.81 codes.

## DISCUSSION

CIPNM is a common problem for patients who survive critical illness, but its true impact on important clinical outcomes is not well defined. To address this knowledge gap, we performed a large propensity matched study examining adult ICU patients throughout the United States. We demonstrated that the development of CIPNM is strongly associated with longer hospital stays, fewer 28-day hospital free days, fewer 28-day ventilator free days, higher hospitalization charges, and reduced percentage of patients discharged to home. These data expand our knowledge of how CIPNM impacts those who survive critical illness.

Strengths of our study include its large sample size and the diversity of included patients and hospitals, which increases the generalizability of our results. The findings of higher hospitalization charges are important for hospital administrators, and the reduced percentage of patients discharged to home should be helpful information for patients and their families

when discussing prognosis after a diagnosis of CIPNM. Our study design with propensity matching and adjustment for unbalanced covariates limits, although does not eliminate, confounders that could impact the relationship between a discharge diagnosis of CIPNM and patient outcomes. By only including patients who had CIPNM coded at the time of discharge (and not at the time of admission), we identified a population of patients who developed CIPNM during their index hospitalization. Finally, although a prior study used ICD-9 codes 357.82 and 359.81 to identify CIPNM in a pediatric population (25), we validated the specificity of these ICD-9 codes to confirm that they identified the correct adult patient population in our analysis.

Although our findings of adverse patient outcomes associated with a discharge diagnosis of CIPNM are consistent with prior research, the unexpected finding of lower mortality in propensity matched patients with a discharge diagnosis of CIPNM requires further exploration. Some, but not all, studies have shown an association between ICUAW/CIPNM and higher hospital mortality (7, 10, 17, 19). Our unexpected finding could be explained by survivor bias, as many of the sickest patients who were most likely to develop CIPNM would have died before a diagnosis of CIPNM could be made, so they could not be included in the group with a discharge diagnosis of CIPNM. As in any observational study, unmeasured confounders (such as illness severity score or level of inflammation) could explain the mortality difference between the groups. CIPNM as a term includes more specific diagnoses (e.g. critical illness polyneuropathy, critical illness myopathy), and it is possible that these more specific disease entities have different relationships with in-hospital mortality. When we added receipt of PT and OT to the propensity model the mortality difference was attenuated. This may be because patients who live long enough to receive PT and OT have lower in-hospital mortality, patients who are less sick and less likely to die may have increased ability to do PT and OT, or we may be selecting for hospitals where the providers are more likely to order PT and OT and also produce better patient outcomes. Finally, another provocative explanation for the lower mortality in CIPNM patients could be differing clinician management. Physicians (or families) who identify a patient as having CIPNM may be more likely to continue aggressive care at the acute care hospital rather than transition to comfort measures since the patient has a potentially reversible process explaining their debility. Further research will be necessary to confirm these findings.

Our study has several limitations. The ICD-9 codes used in this study are likely more specific than sensitive for identifying patients with CIPNM as many affected patients are not diagnosed or that diagnosis is not recorded as an ICD-9 code. Also, since most patients with CIPNM did not undergo NCS/EMG for electrophysiologic diagnosis, we cannot confirm that the discharge diagnosis was correct. Many of the patients coded as having CIPNM likely just had ICUAW (or at least we can’t confirm which subtype of ICUAW such as CIPNM or deconditioning). However, any misclassification of patients would likely bias our results towards the null, and we did validate a high positive predictive value of our included ICD-9 codes in a separate cohort. We showed that our ICD-9 codes were specific for identifying patients with documented weakness and/or abnormal NCS/EMG, and therefore the discharge diagnosis of CIPNM could be a surrogate measure of ICUAW, in the forms of both deconditioning and CIPNM. Despite exclusion of patients with non-CIPNM neuromuscular conditions, propensity matching, and statistical adjustments for unbalanced

covariates, there may still be residual or unmeasured confounding influencing our results and we cannot prove causality with our study design. Given the limitations of this national database, we could not match patients on illness severity score at ICU admission. However, we could match patients on important markers of illness severity including mechanical ventilation, vasopressor use and organ failure. Although both illness severity and pre-morbid patient characteristics are important for patient outcomes (26, 27), recent data indicate that admission diagnosis and illness severity score become less important for patient outcomes than pre-morbid patient characteristics after a prolonged ICU stay, which is a major reason we included ICU LOS in the propensity match model (28). Most patients in the matched CIPNM and non-CIPNM groups had an ICU LOS longer than 10 days, which is the transition point at which admission diagnosis and illness severity no longer predict outcome better than pre-ICU baseline patient characteristics (which were included in our model). In addition, our extensive propensity matching, including matching on ICU LOS, may have produced conservative estimates on the impact of CIPNM on outcomes.

## CONCLUSIONS

In a large propensity matched analysis, we found that a discharge diagnosis of CIPNM is associated with a multitude of outcomes affecting patients both during and after their index hospitalization. Future prospective studies should focus on development of therapies to prevent and treat CIPNM and improve the outcomes of these patients.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Source of funding:** Dr. Moss has received grant funding from the National Institutes of Health, K24 HL089223 and R01 NR011051

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**Table 1**

Patient Outcomes

| Binary Outcomes | CIPNM Subjects n (%) | Non-CIPNM Subjects n (%) | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **In hospital mortality** | | | | |
| Unadjusted Model | 497/3,567 (13.9%) | 180,472/2,807,147 (6.4%) | OR: 2.36 (2.14–2.59) | <.0001 |
| Matched Subjects: Unadjusted Model | 472/3,436 (13.7%) | 630/3,436 (18.3%) | OR: 0.7 (0.62–0.8) | <.0001 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **472/3,436 (13.7%)** | **630/3,436 (18.3%)** | **OR: 0.69 (0.6–0.79)** | **<.0001** |
| **Discharge location (home vs elsewhere)** | | | | |
| Unadjusted Model | 545/3,567 (15.3%) | 1,911,455/2,807,147 (68.1%) | OR: 0.09 (0.08–0.09) | <.0001 |
| Matched Subjects: Unadjusted Model | 527/3,436 (15.3%) | 1,128/3,436 (32.8%) | OR: 0.35 (0.31–0.4) | <.0001 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **527/3,436 (15.3%)** | **1,128/3,436 (32.8%)** | **OR: 0.35 (0.31–0.4)** | **<.0001** |
| **Readmitted within 30 days of discharge** | | | | |
| Unadjusted Model | 315/3,567 (8.83%) | 152,764/2,807,147 (5.44%) | OR: 1.68 (1.5–1.89) | <.0001 |
| Matched Subjects: Unadjusted Model | 305/3,436 (8.88%) | 273/3,436 (7.95%) | OR: 1.13 (0.95–1.34) | 0.16 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **305/3,436 (8.88%)** | **273/3,436 (7.95%)** | **OR: 1.13 (0.95–1.35)** | **0.16** |
| **Continuous Outcomes** | **CIPNM Subjects Mean (StdErr)** | **Non-CIPNM Subjects Mean (StdErr)** | **Difference (95% CI)** | **p-value** |
| **Hospital days** | | | | |
| Unadjusted Model | 31.77 (0.15) | 6.89 (0.005) | 24.87 (24.59–25.16) | <.0001 |
| Matched Subjects: Unadjusted Model | 31.23 (0.45) | 25 (0.42) | 6.22 (5.13–7.32) | <.0001 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **29.59 (0.39)** | **23.81 (0.35)** | **5.78 (4.76–6.8)** | **<.0001** |
| **28-day hospital free days** | | | | |
| Unadjusted Model | 5.33 (0.13) | 19.31 (0.005) | −13.98 (−14.23–13.74) | <.0001 |
| Matched Subjects: Unadjusted Model | 5.52 (0.12) | 6.82 (0.14) | −1.3 (−1.56–1.04) | <.0001 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **6.03 (0.1)** | **7.41 (0.11)** | **−1.38 (−1.62–1.14)** | **<.0001** |
| **28-day ventilator free days** | | | | |
| Unadjusted Model | 13.79 (0.12) | 25.41 (0.004) | −11.62 (−11.85–11.38) | <.0001 |
| Matched Subjects: Unadjusted Model | 14.15 (0.17) | 16 (0.19) | −1.84 (−2.25–1.44) | <.0001 |

*Crit Care Med*. Author manuscript; available in PMC 2018 December 01.

| Binary Outcomes | CIPNM Subjects n (%) | Non-CIPNM Subjects n (%) | Odds Ratio (95% CI) | p-value |
|---|---|---|---|---|
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **15.67 (0.16)** | **17.51 (0.18)** | **−1.84 (−2.24–1.44)** | **<.0001** |
| **Total cost US $** | | | | |
| Unadjusted Model | $355,219.61 ($1,734.28) | $79,230.97 ($61.82) | $275,988.63 ($272,587.34–$279,389.92) | <.0001 |
| Matched Subjects: Unadjusted Model | $347,369.67 ($5,815.62) | $285,286.87 ($4,970.28) | $62,082.81 ($48,549.53–$75,616.09) | <.0001 |
| **Matched Subjects: Model Adjusted using Unbalanced Covariates** | **$313,507.68 ($4,852.56)** | **$256,287.96 ($4,470.02)** | **$57,219.72 ($44,626.05–$69,813.39)** | **<.0001** |

After propensity matching, ICU LOS and pre-ICU hospital LOS remained unbalanced covariates, which required further statistical adjustment to achieve balance between the groups. CI = Confidence interval; CIPNM = Critical illness polyneuromyopathy