Research Square

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Outcomes of Pneumococcal Disease in Patients With B-Cell and Hematological Neoplasms: A Retrospective Cohort Study

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Abstract

Background:

Streptococcus pneumoniae remains a major cause of pneumonia, sepsis, and meningitis, posing particular risk to immunocompromised adults. Patients with hematologic malignancies especially B-cell neoplasms experience profound humoral immune dysfunction and treatment-related B-cell depletion, predisposing them to invasive pneumococcal disease (IPD). Despite this, current vaccination guidelines do not differentiate between hematologic malignancy subtypes, leaving uncertainty regarding optimal prevention strategies. We aimed to characterize the burden and outcomes of pneumococcal disease among adults with hematologic malignancies, focusing on B-cell neoplasms, and to generate evidence supporting refinement of pneumococcal vaccination strategies for this high-risk group.

Methods:

We conducted a retrospective, nationally representative analysis of U.S. hospitalizations for pneumococcal disease from 2018–2021 using the National Inpatient Sample. Weighted multivariable logistic and linear regression models were used to assess associations between hematologic malignancy, particularly B-cell neoplasms, and outcomes including in-hospital mortality, need for invasive mechanical ventilation, length of stay, and hospital charges.

Results:

Among an estimated 186,860 adult pneumococcal hospitalizations, hematologic malignancy was independently associated with increased odds of mechanical ventilation (adjusted OR 1.87, 95% CI 1.73–2.02, $p < 0.001$) and greater healthcare utilization, but not with higher in-hospital mortality (OR 0.95, 95% CI 0.86–1.05). Sensitivity analyses limited to B-cell malignancies yielded consistent results. Acute sepsis physiology, comorbidity burden, and socioeconomic disadvantage were the dominant predictors of adverse outcomes.

Conclusions:

Hematologic and B-cell malignancies significantly amplify the clinical and economic burden of pneumococcal disease, highlighting an urgent need to strengthen pneumococcal vaccination efforts in these populations. Despite comparable in-hospital mortality, the elevated risk of severe respiratory failure and prolonged hospitalization underscores the importance of optimized prevention. Expanding vaccine uptake through routine screening, inpatient vaccination initiatives, and adherence to updated PCV/PPV guidelines should be a public health priority to mitigate preventable morbidity, mortality, and healthcare costs.

Trial registration

Not applicable. This study was a retrospective observational analysis of a deidentified administrative database and did not involve prospective enrollment or intervention.

Introduction

Streptococcus pneumoniae remains a leading cause of community-acquired pneumonia, sepsis, and meningitis, particularly in immunocompromised adults [1, 2]. Patients with hematologic malignancies are at heightened risk for invasive pneumococcal disease due to profound and prolonged immune dysfunction [3, 4]. Among these, B-cell neoplasms—including lymphomas, leukemias, and plasma cell disorders—are uniquely associated with impaired humoral immunity, hypogammaglobulinemia, and treatment-related B-cell depletion from agents such as rituximab, BTK inhibitors, and CAR-T therapies [5–7].

Despite this well-recognized vulnerability, current pneumococcal vaccination guidelines do not distinguish between hematologic malignancy subtypes [8, 9]. Existing recommendations group all hematologic cancers under a single high-risk category, without accounting for the differential immune impairment associated with B-cell–directed disease or therapy [10]. This gap leaves clinicians without clear evidence to guide vaccination timing or strategy in patients most likely to mount suboptimal vaccine responses [11, 12].

While prior studies have examined pneumococcal disease in general hematologic malignancies [13, 14], population-level data specifically characterizing outcomes among patients with B-cell neoplasms are lacking [15]. Understanding the real-world burden and severity of pneumococcal infections in this subgroup is essential to inform risk stratification and vaccination policy [16].

To address this knowledge gap, we evaluated outcomes of pneumococcal disease among adults with hematologic malignancies, focusing on B-cell neoplasms using a large cohort of hospitalized adults in the United States. We compared in-hospital mortality, need for mechanical ventilation, and healthcare utilization between patients with and without B-cell malignancies. Our goal was to provide evidence to support refinement of pneumococcal vaccination strategies for this uniquely vulnerable population.

Methods

Study Design and Data Source

We conducted a retrospective, observational cohort study using data from the National Inpatient Sample (NIS) for the years 2018–2021. The NIS, part of the Healthcare Cost and Utilization Project (HCUP), is the largest publicly available, all-payer inpatient database in the United States. [17] It captures approximately 20% of annual community hospital discharges and includes discharge-level data with survey weights, stratification, and clustering variables, enabling nationally representative estimates.

Study Population

We identified adult hospitalizations (≥ 19 years) with a principal diagnosis of pneumococcal disease, defined by *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* [18]

codes for pneumococcal pneumonia or invasive pneumococcal disease (septicemia or meningitis; Supplementary Table 1). Hospitalizations with missing data were excluded.

Pneumococcal disease was identified using ICD-10-CM codes for pneumococcal pneumonia and invasive pneumococcal disease, including pneumococcal septicemia and meningitis (Supplementary Table 1). A principal diagnosis of pneumococcal disease was required to capture hospitalizations primarily attributable to pneumococcal infection. Invasive pneumococcal disease codes were captured regardless of secondary diagnosis position when present.

Hospitalizations were categorized into two cohorts:

1. **Hematologic malignancy cohort (exposed group)**: Cases with a secondary diagnosis of acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, or multiple myeloma (Supplementary Table 1).
2. **Non-hematologic malignancy cohort (comparator group)**: Cases without any hematologic malignancy. Hospitalizations with solid-organ cancers but no hematologic malignancy were included in this group.

Because the NIS is discharge-based, each record was treated as an independent hospitalization, and survey discharge weights were applied to obtain national estimates.

Outcomes

The primary outcome was in-hospital mortality. The key secondary outcome was the need for invasive mechanical ventilation during hospitalization. Additional secondary outcomes included hospital length of stay (days) and total hospitalization charges (USD). Prespecified sensitivity analyses were performed restricting the exposure group to patients with B-cell hematologic malignancies to assess the robustness of associations with mortality, mechanical ventilation, length of stay, and total charges. Total hospital charges, rather than costs, were analyzed because cost-to-charge ratio files were not applied; charges were used as a consistent proxy for relative healthcare resource utilization across hospitalizations.

Covariates

We adjusted for demographic, clinical, and hospital-level factors that could confound the relationship between hematologic malignancy and outcomes. Patient-level variables included age, sex, race/ethnicity, insurance type, and the Charlson Comorbidity Index Quan Modification (CCI) [19], derived from secondary diagnoses. Calendar year of admission was included to account for temporal trends. Sepsis and severe sepsis were identified using validated ICD-10-CM diagnosis codes. ‘Any sepsis’ captured hospitalizations with sepsis without shock, while ‘severe sepsis’ included cases with documented acute organ dysfunction with or without septic shock. Both variables were retained in multivariable models to distinguish baseline infection severity from progression to organ dysfunction. Collinearity diagnostics demonstrated acceptable variance inflation factors for all covariates.

Statistical Analysis

Survey discharge weights were incorporated to generate national estimates from the NIS. Descriptive statistics were calculated for study cohorts, with means or medians for continuous variables and proportions for categorical variables.

For binary outcomes (in-mortality & mechanical ventilation), we used weighted binary logistic regression models with a odds ratio (OR), coefficients and 95% confidence intervals (CIs). Results were expressed as multiplicative effects (OR for logistic regression and coefficient-B). Models were adjusted for all clinical and demographic covariates which could potentially be confounders.

A sensitivity analysis was conducted restricting the hematologic malignancy group to B-cell neoplasms (e.g., follicular lymphoma [C82.*], diffuse large B-cell lymphoma [C83.3], mantle cell lymphoma [C83.1], Burkitt lymphoma [C83.7], chronic lymphocytic leukemia [C91.1], hairy cell leukemia [C91.4], Waldenström macroglobulinemia [C88.0], and multiple myeloma/plasma cell neoplasms [C90.*]; Supplementary Table S1) to assess associations with mechanical ventilation and in-hospital mortality. All analyses incorporated the National Inpatient Sample survey design, including discharge weights, hospital stratification, and clustering variables, in accordance with Healthcare Cost and Utilization Project (HCUP) analytic recommendations, to generate nationally representative estimates. Hospitalizations with missing data for age, sex, mortality status, or discharge disposition (< 2% of records) were excluded from analyses.

Ethical Considerations

The study was exempt from institutional review board approval because the NIS contains de-identified data. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in study design and reporting.

Limitations

This study had several limitations. As an ICD-10 code–based analysis, it is subject to potential misclassification and coding errors. The NIS lacks detailed clinical information such as laboratory data, microbiologic confirmation, treatment regimens, and vaccination history, limiting the ability to assess disease severity or prior pneumococcal immunization. Because the database is discharge-based, longitudinal follow-up and readmission data are unavailable, and each hospitalization was treated as an independent event. Despite adjustment for multiple confounders, residual confounding from unmeasured variables such as chemotherapy status or immunosuppressive therapy may persist. Additionally, variations in coding and care practices across hospitals may affect generalizability, and the retrospective design precludes causal inference.

Results

Cohort Characteristics

From 2018 through 2021, an estimated 186,860 weighted hospitalizations for pneumococcal disease were identified among adults aged ≥ 19 years in the National Inpatient Sample. The mean patient age was 63.2 years (SD ± 16.0), and 52.3% were female. The cohort exhibited a substantial comorbidity burden, with a mean Charlson Comorbidity Index (CCI) of 2.3 (SD ± 2.3). The most prevalent comorbidities were chronic pulmonary disease (45.3%), congestive heart failure (27.7%), and diabetes without complications (21.2%). Most patients were insured through Medicare (53.6%), and more than one-third resided in ZIP codes within the lowest national quartile for median household income. The median hospital length of stay was 6 days (IQR, 4–11), while the mean was 9.1 days, suggesting a right-skewed distribution with a subset of prolonged admissions. The median total hospital charges were $55,458 (IQR, $29,057–$118,757), with a mean of $111,762 (SD ±$190,504), reflecting substantial variability in economic burden. (Table 1)
Although unadjusted analyses demonstrated a lower crude prevalence of invasive mechanical ventilation among patients with hematologic malignancies (Table 1), this association reversed after multivariable adjustment, reflecting substantial confounding by age, baseline pulmonary disease, smoking prevalence, and comorbidity burden, all of which were less prevalent in the hematologic malignancy cohort.

Table 1
Baseline Characteristics (weighted) of Adults Hospitalized with Pneumococcal Disease (2018–2021)

Variable	Non-Hematologic Malignancy Cohort	Hematologic Malignancy
Died during hospitalization	14,310 (8.0%)	585 (7.4%)
Female	86,035 (48.1%)	3,035 (38.6%)
Primary expected payer		
Medicaid	35,935 (20.1%)	885 (11.3%)
Private insurance	32,405 (18.1%)	1,800 (22.9%)
Self-pay	9,755 (5.4%)	115 (1.5%)
No charge	600 (0.3%)	5 (0.1%)
Other insurance	4,850 (2.7%)	210 (2.7%)
Race		
White	122,665 (70.4%)	5,250 (68.8%)
Black	26,675 (15.3%)	1,200 (15.7%)
Hispanic	15,050 (8.6%)	710 (9.3%)
Asian/Pacific Islander	3,200 (1.8%)	175 (2.3%)
Native American	2,695 (1.5%)	35 (0.5%)
Other	3,950 (2.3%)	260 (3.4%)
Median household income quartile (ZIP)		
Q1 (lowest)	63,115 (36.2%)	2,190 (28.4%)
Q2	48,670 (27.9%)	2,135 (27.7%)
Q3	38,055 (21.9%)	1,930 (25.0%)
Q4 (highest)	24,305 (14.0%)	1,455 (18.9%)
Myocardial infarction	20,065 (11.2%)	710 (9.0%)
Congestive heart failure	49,620 (27.7%)	2,090 (26.6%)
Peripheral vascular disease	12,360 (6.9%)	520 (6.6%)
Chronic pulmonary disease	82,230 (45.9%)	2,360 (30.0%)
Rheumatic disease	7,350 (4.1%)	225 (2.9%)
Mild liver disease	12,665 (7.1%)	265 (3.4%)

Variable	Non-Hematologic Malignancy Cohort	Hematologic Malignancy
Diabetes without complications	38,305 (21.4%)	1,350 (17.2%)
Diabetes with complications	22,645 (12.7%)	900 (11.5%)
Renal disease	33,925 (19.0%)	2,020 (25.7%)
Moderate/severe liver disease	4,635 (2.6%)	90 (1.1%)
Metastatic solid tumor	5,805 (3.2%)	300 (3.8%)
AIDS/HIV	4,195 (2.3%)	135 (1.7%)
Severe sepsis (with/without shock)	57,305 (32.0%)	2,560 (32.6%)
Ventilator procedure performed	42,675 (23.8%)	1,070 (13.6%)
Smoker	52,225 (29.2%)	1,065 (13.5%)
Alcohol user	8,315 (4.6%)	75 (1.0%)
Any sepsis	32,100 (17.9%)	1,375 (17.5%)
B-cell hematologic malignancy present	—	5,400 (68.7%)
Age, years (mean ± SD)	62.8 ± 16.1	66.9 ± 13.8
Length of stay, days (mean ± SD)	9.1 ± 10.4	9.5 ± 11.8
Total charges (USD, mean ± SD)	112,781 ± 193,070	108,244 ± 155,167
Calendar year (mean ± SD)	2019.28 ± 1.08	2019.24 ± 1.06
Charlson Comorbidity Index (mean ± SD)	2.48 ± 2.28	2.17 ± 2.24

Primary Outcomes:

After multivariable adjustment for demographic, socioeconomic, and clinical covariates, hematologic malignancy was independently associated with higher odds of invasive mechanical ventilation (OR 1.87, 95% CI 1.73–2.02; $p < 0.001$) but not with in-hospital mortality (OR 0.95, 95% CI 0.86–1.05; $p = 0.285$). Markers of acute illness and comorbidity were dominant predictors of adverse outcomes. Sepsis (OR 7.78 for ventilation; 2.30 for mortality), severe sepsis (OR 1.24; 1.60), and a higher CCI (OR 1.55; 1.03) were each strongly associated with increased risk. Ventilator use was the single strongest predictor of mortality (OR 8.19, 95% CI 7.83–8.56). Socioeconomic gradients were evident, with Medicaid and self-pay patients experiencing higher mortality compared with those insured through Medicare or private insurance. Collectively, these findings indicate that acute physiological derangement, underlying comorbidity, and systemic illness severity, rather than malignancy status alone, primarily determine outcomes among hospitalized patients with pneumococcal infection. (Table 2, Fig. 1)

Table 2
Multivariable Logistic Regression Analysis of Factors Associated with Mechanical Ventilation and In-Hospital Mortality Among Patients With Hematologic Malignancy

Variable	In-Hospital Mortality OR (95% CI)	p-value	Mechanical Ventilation OR (95% CI)	p-value
Age at admission (per year)	**1.038 (1.036–1.040)**	**< 0.001**	**0.975 (0.973–0.977)**	**< 0.001**
Female (vs male)	1.018 (0.978–1.059)	0.385	**0.802 (0.782–0.823)**	**< 0.001**
Primary expected payer (vs Medicare)		**< 0.001**		**< 0.001**
Medicaid	**1.184 (1.112–1.261)**	**< 0.001**	**1.266 (1.217–1.317)**	**< 0.001**
Private insurance	**1.101 (1.036–1.170)**	**0.002**	1.017 (0.978–1.058)	0.383
Self-pay	**1.559 (1.417–1.715)**	**< 0.001**	**1.084 (1.022–1.150)**	**0.008**
No charge	**1.635 (1.188–2.251)**	**0.003**	1.044 (0.842–1.295)	0.696
Other insurance	**1.451 (1.292–1.630)**	**< 0.001**	1.077 (0.996–1.165)	0.065
Race (vs White)		**< 0.001**		0.012
Black	**0.927 (0.874–0.983)**	**0.013**	0.998 (0.962–1.036)	0.906
Hispanic	**1.134 (1.059–1.215)**	**< 0.001**	**0.942 (0.901–0.986)**	**0.011**
Asian/Pacific Islander	1.118 (0.981–1.275)	0.094	1.005 (0.917–1.102)	0.917
Native American	**1.200 (1.032–1.396)**	**0.018**	**1.145 (1.034–1.267)**	**0.009**
Other	0.900 (0.793–1.021)	0.103	1.018 (0.936–1.108)	0.674
Calendar year (per year)	**1.316 (1.293–1.340)**	**< 0.001**	**1.112 (1.099–1.125)**	**< 0.001**
Median household income (vs Quartile 1)		**0.005**		**< 0.001**
Quartile 2	**0.922 (0.876–0.970)**	**0.001**	**0.884 (0.857–0.913)**	**< 0.001**
Quartile 3	0.991 (0.940–1.045)	0.749	**0.836 (0.807–0.866)**	**< 0.001**
Quartile 4	1.009 (0.948–1.074)	0.772	**0.749 (0.717–0.781)**	**< 0.001**
Chronic pulmonary disease	**0.739 (0.703–0.777)**	**<**	**0.629 (0.610–0.649)**	**<**

Variable	In-Hospital Mortality OR (95% CI)	p-value	Mechanical Ventilation OR (95% CI)	p-value
Age at admission (per year)	**1.038 (1.036–1.040)**	**< 0.001**	**0.975 (0.973–0.977)**	**< 0.001**
		0.001		**0.001**
Rheumatic disease	0.933 (0.836–1.042)	0.218	**0.436 (0.405–0.470)**	**< 0.001**
Congestive heart failure	1.035 (0.984–1.089)	0.190	**0.938 (0.905–0.972)**	**< 0.001**
Myocardial infarction	**1.119 (1.053–1.189)**	**< 0.001**	1.018 (0.975–1.063)	0.428
Diabetes without complications	**0.874 (0.827–0.923)**	**< 0.001**	**0.769 (0.742–0.796)**	**< 0.001**
Diabetes with complications	**0.910 (0.837–0.990)**	**0.027**	**0.396 (0.374–0.420)**	**< 0.001**
Renal disease	**1.132 (1.048–1.223)**	**0.002**	**0.329 (0.311–0.348)**	**< 0.001**
Moderate/severe liver disease	**2.538 (2.239–2.877)**	**< 0.001**	**0.338 (0.307–0.373)**	**< 0.001**
Metastatic solid tumor	**2.533 (2.112–3.039)**	**< 0.001**	**0.052 (0.045–0.059)**	**< 0.001**
AIDS/HIV	0.958 (0.757–1.212)	0.723	**0.027 (0.024–0.032)**	**< 0.001**
Charlson Comorbidity Index	**1.030 (1.003–1.058)**	**0.030**	**1.551 (1.521–1.582)**	**< 0.001**
Severe sepsis (with/without shock)	**1.599 (1.503–1.702)**	**< 0.001**	**1.245 (1.199–1.292)**	**< 0.001**
Ventilator procedure performed	**8.193 (7.813–8.593)**	**< 0.001**	—	—
Smoker	**0.650 (0.617–0.685)**	**< 0.001**	0.988 (0.959–1.018)	0.443
Alcohol user	1.065 (0.969–1.170)	0.191	**1.144 (1.080–1.210)**	**< 0.001**
Any Sepsis	**2.300 (2.161–2.448)**	**< 0.001**	**7.743 (7.430–8.067)**	**< 0.001**
Hematologic malignancy (vs none)	0.947 (0.857–1.046)	0.285	**1.871 (1.704–2.057)**	**< 0.001**
Constant	**0.000 (0.000–0.000)**	**< 0.001**	**0.000 (0.000–0.000)**	**< 0.001**

Figure 1:Forest Plots of Adjusted Odds Ratios for Ventilator Use and In-Hospital Mortality Among Hospitalized Patients With Hematologic Malignancy

Secondary Outcomes:

In adjusted linear regression models, hematologic malignancy was significantly associated with both prolonged hospital stay (B = 1.20 days, $p < 0.001$) and greater total hospital charges (B = $11,085, $p < 0.001$), underscoring its contribution to resource utilization. Additional drivers of increased utilization included sepsis, ventilator use, and higher comorbidity burden (CCI; all $p < 0.001$). Conversely, patients with chronic pulmonary disease, renal disease, or metastatic solid tumors exhibited shorter stays and lower adjusted charges, possibly reflecting early mortality or limitations in therapeutic intensity. These results collectively suggest that hematologic malignancies impose a substantial clinical and financial impact on hospital care, largely mediated through critical illness severity and comorbidity complexity. (Table 3)

Table 3
Multivariable Linear Regression Analysis of Factors Associated with Hospital Length of Stay and Total Charges in Patients with Hematologic Malignancies

Variable	Length of Stay			Total Charges		
	OR (B)	95% CI	P-value	OR (B)	95% CI	P-value
Age in years at admission	-0.028	-0.031 – -0.024	< .001	-788.763	-849.205 – -728.321	< .001
Indicator of sex	-0.246	-0.336 – -0.156	< .001	-7998.445	-9615.368 – -6381.522	< .001
Primary expected payer	0.166	0.124– 0.208	< .001	3207.775	2454.434– 3961.115	< .001
Race (uniform)	0.261	0.219– 0.303	< .001	11352.540	10597.021– 12108.058	< .001
Calendar year	0.484	0.443– 0.525	< .001	10999.624	10264.152– 11735.095	< .001
Median household income (ZIP quartile)	0.046	0.003– 0.088	.034	6911.803	6155.550– 7668.056	< .001
Myocardial Infarction	-1.852	-2.016 – -1.688	< .001	-20904.164	-23848.439 – -17959.889	< .001
Congestive Heart Failure	-0.818	-0.948 – -0.688	< .001	-10406.991	-12740.669 – -8073.313	< .001
Chronic Pulmonary Disease	-2.324	-2.439 – -2.209	< .001	-36357.372	-38415.710 – -34299.033	< .001
Rheumatic Disease	-1.664	-1.898 – -1.431	< .001	-32639.854	-36823.423 – -28456.284	< .001
Diabetes w/o complications	-1.433	-1.564 – -1.301	< .001	-21207.144	-23568.622 – -18845.666	< .001
Diabetes w/ complications	-3.326	-3.535 – -3.117	< .001	-48674.163	-52421.001 – -44927.326	< .001
Renal Disease	-2.864	-3.060 – -2.668	< .001	-44166.170	-47680.645 – -40651.696	< .001
Mod/Severe Liver Disease	-4.689	-5.064 – -4.314	< .001	-69075.599	-75799.495 – -62351.704	< .001
Metastatic Solid Tumor	-9.510	-10.005 – -9.015	< .001	-142632.100	-151504.427 – -133759.773	< .001
AIDS/HIV	-8.976	-9.508 – -8.444	< .001	-133379.011	-142942.168 – -123815.854	< .001

Variable	Length of Stay			Total Charges		
	OR (B)	95% CI	P-value	OR (B)	95% CI	P-value
Charlson Comorbidity Index	1.662	1.590–1.734	< .001	23955.172	22662.951–25247.393	< .001
Severe Sepsis	0.443	0.314–0.572	< .001	6490.079	4172.833–8807.324	< .001
Ventilator procedure	8.160	8.041–8.279	< .001	158192.865	156063.363–160322.368	< .001
Smoker	-0.986	-1.091 – -0.880	< .001	-23267.114	-25158.622 – -21375.606	< .001
Alcohol User	0.156	-0.064–0.375	.164	-4064.575	-8012.777 – -116.374	.044
Sepsis (Yes)	1.395	1.229–1.560	< .001	40928.518	37953.418–43903.619	< .001
Hematologic Malignancy (C81–C96)	1.195	0.974–1.416	< .001	11085.456	7126.498–15044.414	< .001

Sensitivity Analyses:

In analyses restricted to B-cell hematologic malignancies, the associations remained directionally consistent. B-cell malignancy was significantly associated with higher odds of mechanical ventilation (OR 1.87, 95% CI 1.73–2.02; $p < 0.001$) but not with in-hospital mortality (OR 0.97, 95% CI 0.86–1.10; $p = 0.629$). Linear regression revealed a significant increase in length of stay (B = 0.69 days, $p < 0.001$) and a marginal, non-significant rise in total charges (B = $4,729, $p = 0.051$). Older age, severe sepsis, and ventilator use were the most powerful predictors of death, while comorbid liver disease and metastatic tumors doubled mortality risk. Lower odds of ventilation were observed in females, older adults, and those with advanced chronic diseases, potentially reflecting treatment limitations. These findings reinforce that acute sepsis physiology and comorbidity burden—rather than the malignancy subtype per se, predominantly influence hospital outcomes. (Table 4–5, Fig. 2)

Table 4

Multivariable Logistic Regression Analysis of Factors Associated With Mechanical Ventilation and In-Hospital Mortality Among Patients With B-Cell Hematologic Malignancy

Variable	OR (Mortality)	95% CI (Mortality)	P (Mortality)	OR (Ventilator)	95% CI (Ventilator)	P (Ventilator)
B-cell hematologic malignancy	0.970	(0.857–1.098)	0.629	**1.870**	**(1.732–2.019)**	**< 0.001**
Age at admission (per year)	**1.038**	**(1.036–1.040)**	**< 0.001**	**0.975**	**(0.973–0.977)**	**< 0.001**
Female (vs male)	1.016	(0.977–1.057)	0.428	**0.800**	**(0.780–0.821)**	**< 0.001**
Primary expected payer (vs Medicare)			**< 0.001**			**< 0.001**
Medicaid	**1.183**	**(1.111–1.260)**	**< 0.001**	**1.263**	**(1.214–1.314)**	**< 0.001**
Private insurance	**1.101**	**(1.036–1.170)**	**0.002**	1.019	(0.980–1.059)	0.340
Self-pay	**1.556**	**(1.414–1.712)**	**< 0.001**	**1.076**	**(1.015–1.141)**	**0.015**
No charge	**1.631**	**(1.185–2.245)**	**0.003**	1.035	(0.833–1.285)	0.754
Other insurance	**1.450**	**(1.291–1.629)**	**< 0.001**	1.072	(0.991–1.160)	0.083
Race (vs White)			**< 0.001**			**0.015**
Black	**0.928**	**(0.875–0.985)**	**0.014**	1.001	(0.964–1.039)	0.968
Hispanic	**1.135**	**(1.059–1.216)**	**< 0.001**	**0.945**	**(0.903–0.989)**	**0.015**
Asian/Pacific Islander	1.118	(0.981–1.274)	0.093	1.018	(0.929–1.116)	0.708
Native American	**1.199**	**(1.030–1.395)**	**0.019**	**1.142**	**(1.032–1.264)**	**0.010**
Other	0.902	(0.795–1.023)	0.108	1.021	(0.939–1.110)	0.632
Calendar year (per year)	**1.316**	**(1.293–1.340)**	**< 0.001**	**1.112**	**(1.099–1.125)**	**< 0.001**
Median household			**0.005**			**< 0.001**

Variable	OR (Mortality)	95% CI (Mortality)	P (Mortality)	OR (Ventilator)	95% CI (Ventilator)	P (Ventilator)
income (vs Quartile 1)						
Quartile 2	**0.922**	**(0.876–0.970)**	**0.002**	**0.885**	**(0.858–0.913)**	**< 0.001**
Quartile 3	0.992	(0.941–1.046)	0.777	**0.836**	**(0.808–0.865)**	**< 0.001**
Quartile 4	1.010	(0.949–1.075)	0.752	**0.749**	**(0.718–0.781)**	**< 0.001**
Chronic pulmonary disease	**0.738**	**(0.702–0.776)**	**< 0.001**	**0.629**	**(0.610–0.649)**	**< 0.001**
Rheumatic disease	0.933	(0.835–1.042)	0.216	**0.435**	**(0.404–0.468)**	**< 0.001**
Congestive heart failure	1.035	(0.984–1.089)	0.183	**0.941**	**(0.909–0.975)**	**< 0.001**
Myocardial infarction	**1.120**	**(1.053–1.191)**	**< 0.001**	1.020	(0.977–1.064)	0.365
Diabetes without complications	**0.874**	**(0.827–0.924)**	**< 0.001**	**0.769**	**(0.742–0.797)**	**< 0.001**
Diabetes with complications	**0.910**	**(0.836–0.990)**	**0.028**	**0.397**	**(0.374–0.421)**	**< 0.001**
Renal disease	**1.136**	**(1.052–1.227)**	**0.001**	**0.331**	**(0.313–0.350)**	**< 0.001**
Moderate/severe liver disease	**2.542**	**(2.241–2.883)**	**< 0.001**	**0.340**	**(0.309–0.374)**	**< 0.001**
Metastatic solid tumor	**2.547**	**(2.122–3.057)**	**< 0.001**	**0.052**	**(0.045–0.059)**	**< 0.001**
AIDS/HIV	0.962	(0.760–1.217)	0.746	**0.028**	**(0.024–0.032)**	**< 0.001**
Charlson Comorbidity Index	**1.030**	**(1.002–1.058)**	**0.035**	**1.548**	**(1.518–1.579)**	**< 0.001**
Severe sepsis (with/without shock)	**1.600**	**(1.503–1.704)**	**< 0.001**	**1.244**	**(1.198–1.292)**	**< 0.001**
Ventilator procedure performed	**8.178**	**(7.802–8.573)**	**< 0.001**	—	—	—
Smoker	**0.649**	**(0.616–**	**< 0.001**	0.985	(0.956–	0.304

Variable	OR (Mortality)	95% CI (Mortality)	P (Mortality)	OR (Ventilator)	95% CI (Ventilator)	P (Ventilator)
		0.684)			1.014)	
Alcohol user	1.064	(0.968–1.169)	0.201	**1.139**	**(1.076–1.205)**	**< 0.001**
Any Sepsis	**2.301**	**(2.162–2.449)**	**< 0.001**	**7.779**	**(7.469–8.102)**	**< 0.001**
Constant	**0.000**	**(0.000–0.000)**	**< 0.001**	**0.000**	* *	**< 0.001**

Figure 2: Adjusted Odds Ratios for Ventilator Use and In-Hospital Mortality Among Hospitalized Patients With B-Cell Hematologic Malignancy

Table 5
Multiple Linear Regression showing association of B-cell Hematologic Malignancy with Hospital Charges and Length of Stay

Variable	Model: Total Charges (USD)			Model: Length of Stay (Days)		
	B (OR)	95% CI	P-value	B (OR)	95% CI	P-value
Age in years at admission	-785.563	[-846.044, -725.081]	< .001	-0.027	[-0.031, -0.024]	< .001
Indicator of sex	-8127.854	[-9744.913, -6510.795]	< .001	-0.257	[-0.347, -0.167]	< .001
Primary expected payer (uniform)	3187.661	[2434.293, 3941.030]	< .001	0.164	[0.122, 0.206]	< .001
Race (uniform)	11367.129	[10611.575, 12122.684]	< .001	0.263	[0.221, 0.305]	< .001
Calendar year	10996.168	[10260.643, 11731.694]	< .001	0.483	[0.442, 0.524]	< .001
Median household income quartile	6943.940	[6187.680, 7700.201]	< .001	0.049	[0.006, 0.091]	.024
Myocardial infarction	-20845.546	[-23789.957, -17901.136]	< .001	-1.846	[-2.010, -1.682]	< .001
Congestive heart failure	-10326.502	[-12660.199, -7992.806]	< .001	-0.810	[-0.940, -0.680]	< .001
Chronic pulmonary disease	-36435.983	[-38494.615, -34377.350]	< .001	-2.330	[-2.445, -2.215]	< .001
Rheumatic disease	-32650.004	[-36833.918, -28466.090]	< .001	-1.666	[-1.900, -1.432]	< .001
Diabetes w/o complications	-21179.395	[-23541.070, -18817.720]	< .001	-1.430	[-1.562, -1.299]	< .001
Diabetes w/ complications	-48577.950	[-52325.036, -44830.864]	< .001	-3.317	[-3.526, -3.108]	< .001
Renal disease	-43828.932	[-47343.078, -40314.787]	< .001	-2.834	[-3.030, -2.638]	< .001
Moderate/Severe liver disease	-68872.177	[-75596.466, -62147.889]	< .001	-4.671	[-5.046, -4.296]	< .001
Metastatic solid tumor	-141962.169	[-150834.194, -133090.144]	< .001	-9.450	[-9.945, -8.955]	< .001
AIDS/HIV	-132735.772	[-142297.756, -123173.789]	< .001	-8.916	[-9.448, -8.384]	< .001

Variable	Model: Total Charges (USD)			Model: Length of Stay (Days)		
	B (OR)	95% CI	P-value	B (OR)	95% CI	P-value
Charlson Comorbidity Index	23844.881	[22552.836, 25136.927]	< .001	1.652	[1.580, 1.724]	< .001
Severe sepsis (with/without shock)	6487.959	[4170.465, 8805.454]	< .001	0.442	[0.313, 0.571]	< .001
Ventilator	158031.200	[155902.101, 160160.300]	< .001	8.145	[8.026, 8.264]	< .001
Smoker	-23422.605	[-25313.515, -21531.694]	< .001	-1.001	[-1.106, -0.895]	< .001
Alcohol user	-4248.278	[-8196.420, -300.135]	.035	0.139	[-0.081, 0.359]	.215
Any Sepsis	41019.795	[38044.667, 43994.923]	< .001	1.404	[1.238, 1.570]	< .001
B-cell hematologic malignancy	4729.138	[-28.719, 9486.994]	.051	0.690	[0.425, 0.956]	< .001

Discussion

In our study assessing the burden of pneumococcal disease in hematological malignancy patients, we found that hematologic malignancy was associated with a significantly increased likelihood of requiring invasive mechanical ventilation but not with higher in-hospital mortality in patients with pneumococcal diseases. These findings suggest that while patients with hematologic malignancies experience greater clinical severity necessitating advanced respiratory support, hospital-based survival outcomes have improved, likely reflecting advances in critical care, antimicrobial therapy, and supportive oncology practices [20, 21]. The results further demonstrate that the excess morbidity and resource utilization in this population are primarily mediated through sepsis, multiorgan dysfunction, and comorbidity burden rather than malignancy status alone.

Our findings align with prior reports indicating that hematologic malignancy predisposes to severe pneumococcal infections due to impaired humoral and cellular immunity, particularly in the context of B-cell–directed therapies, stem cell transplantation, or chemotherapy-induced cytopenias [22, 23]. However, the lack of a corresponding increase in adjusted mortality observed in our study may reflect improvements in pneumococcal vaccination coverage, earlier recognition of sepsis, and refined intensive care protocols for immunocompromised hosts [24, 25]. The observed 1.9-fold higher odds of mechanical ventilation among patients with hematologic malignancy underscore the clinical fragility of this population and the heightened risk of respiratory failure secondary to sepsis or pneumonia. Nonetheless, the absence of

excess mortality suggests that once critical illness develops, outcomes may be comparable to those of nonmalignant counterparts when equitable access to intensive care is achieved.

The increased likelihood of invasive mechanical ventilation observed among patients with hematologic malignancies has implications that extend beyond acute infection severity. In this population, critical illness frequently disrupts planned chemotherapy schedules, delays disease-directed therapy, and contributes to downstream complications such as prolonged cytopenias, secondary infections, and functional decline. Intensive care utilization in patients with hematologic malignancies is also associated with higher financial toxicity, increased caregiver burden, and reduced treatment tolerance, underscoring the importance of preventing severe respiratory complications in this vulnerable group.

The secondary analyses provide further insight into health system impacts. Patients with hematologic malignancy incurred significantly longer hospital stays and greater total charges, reflecting the cumulative effect of disease complexity, infection severity, and resource-intensive management. The incremental cost burden mirrors prior studies documenting increased hospitalization expenditures among immunocompromised adults with community-acquired pneumonia and sepsis [26, 27]. Importantly, comorbid conditions such as severe liver disease, metastatic solid tumors, and renal dysfunction emerged as strong independent predictors of both mortality and prolonged hospitalization, emphasizing the multifactorial nature of poor outcomes in pneumococcal disease. Conversely, lower mortality observed among patients with chronic pulmonary disease and diabetes, though counterintuitive, may reflect differential coding practices, earlier healthcare engagement, or competing risk phenomena rather than protective biological effects [28, 29].

Our results also highlight persistent socioeconomic gradients in outcomes. Lower household income and lack of insurance coverage were associated with higher odds of adverse outcomes and greater resource utilization, consistent with prior literature linking socioeconomic disadvantage to delays in presentation, lower vaccination uptake, and disparities in access to specialized care [30, 31]. Although vaccination status could not be ascertained within the National Inpatient Sample, the observed burden of severe pneumococcal disease among patients with hematologic and B-cell malignancies supports prioritization of pneumococcal vaccine uptake and system-level prevention strategies in this population. Our findings reinforce the importance of targeted prevention strategies—including pneumococcal vaccination, outpatient infection surveillance, and equitable inpatient resource allocation—among socioeconomically vulnerable and immunocompromised populations.

The sensitivity analysis restricted to B-cell malignancies strengthens the robustness of our conclusions. Despite their profound immunologic vulnerability, patients with B-cell neoplasms did not demonstrate significantly higher in-hospital mortality compared with other malignancies, suggesting that disease-specific factors, such as targeted therapy–related hypogammaglobulinemia, may contribute more to infection risk than to mortality once hospitalized [32, 33]. Nonetheless, these patients remained at higher risk of requiring ventilatory support and extended hospitalization, underscoring the need for proactive infection control measures and optimized early management protocols.

This study expands the limited body of literature examining pneumococcal disease outcomes in hematologic malignancies within a contemporary, post-vaccine era context. Unlike single-center or registry-based reports, our use of the National Inpatient Sample provides a comprehensive and generalizable national estimate encompassing diverse care settings, payer types, and demographic strata [34]. The consistency of our findings across sensitivity analyses enhances internal validity and underscores the stability of observed associations.

However, several limitations merit consideration. As an administrative database analysis, misclassification bias due to diagnostic coding cannot be excluded [35]. The NIS lacks granular data on microbiologic confirmation, vaccination status, and treatment regimens, precluding evaluation of vaccine-preventable disease burden or therapy-specific effects [36]. Furthermore, the cross-sectional nature of the data limits inference on temporal relationships or long-term outcomes beyond hospitalization. Despite rigorous adjustment, residual confounding from unmeasured variables such as chemotherapy timing, neutropenia, or corticosteroid exposure is likely [37]. Finally, while the study period includes the early COVID-19 era, diagnostic overlap and changes in hospital admission patterns may have influenced case capture and outcome measures [38].

Conclusion

Hematologic malignancies are associated with a substantially greater clinical and economic burden of pneumococcal disease, characterized by longer hospitalizations, increased need for invasive mechanical ventilation, and higher healthcare resource utilization despite comparable in-hospital mortality. These findings highlight the heightened vulnerability of immunocompromised cancer populations to severe pneumococcal infection and underscore persistent gaps in preventive care. Although vaccination status could not be directly assessed, the observed burden of severe disease supports the prioritization of pneumococcal immunization strategies in patients with hematologic malignancies in accordance with current CDC and ACIP recommendations. System-level interventions, including routine assessment of vaccination status, inpatient vaccination initiatives, and electronic health record–based reminders may help mitigate preventable morbidity, reduce healthcare utilization, and improve supportive care outcomes in this high-risk population.

Abbreviations

ACIP
Advisory Committee on Immunization Practices
BTK–Bruton tyrosine kinase
CAR–T–Chimeric antigen receptor T–cell
CCI–Charlson Comorbidity Index
CDC–Centers for Disease Control and Prevention
CI–Confidence interval
HCUP–Healthcare Cost and Utilization Project
ICD–10–CM–International Classification of Diseases

Tenth Revision
Clinical Modification
IPD
Invasive pneumococcal disease
LOS–Length of stay
NIS–National Inpatient Sample
OR–Odds ratio
PCV–Pneumococcal conjugate vaccine
PPV–Pneumococcal polysaccharide vaccine
SD–Standard deviation
STROBE–Strengthening the Reporting of Observational Studies in Epidemiology
USD–United States dollars

Declarations

Ethics approval and consent to participate:

Not applicable. This study used de-identified, publicly available data from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample. In accordance with institutional and federal regulations, analyses of de-identified administrative datasets do not constitute human subjects research and are exempt from institutional review board review.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Large language model (LLM) use disclosure

A commercial language editing tool (Grammarly®) was used solely for grammar, spelling, and stylistic refinement. No large language model was used for study design, data analysis, data interpretation, or generation of scientific content. All authors take full responsibility for the integrity and accuracy of the manuscript.

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Author Contribution

MP and KS conceived the study and developed the study design. MP and KS performed the statistical analyses. MP drafted the initial manuscript. KS, VG, LK, and AD critically reviewed and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Data Availability

The data analyzed in this study are publicly available from the Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS), Agency for Healthcare Research and Quality. The datasets are available to qualified researchers following completion of the HCUP Data Use Agreement.

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Figures

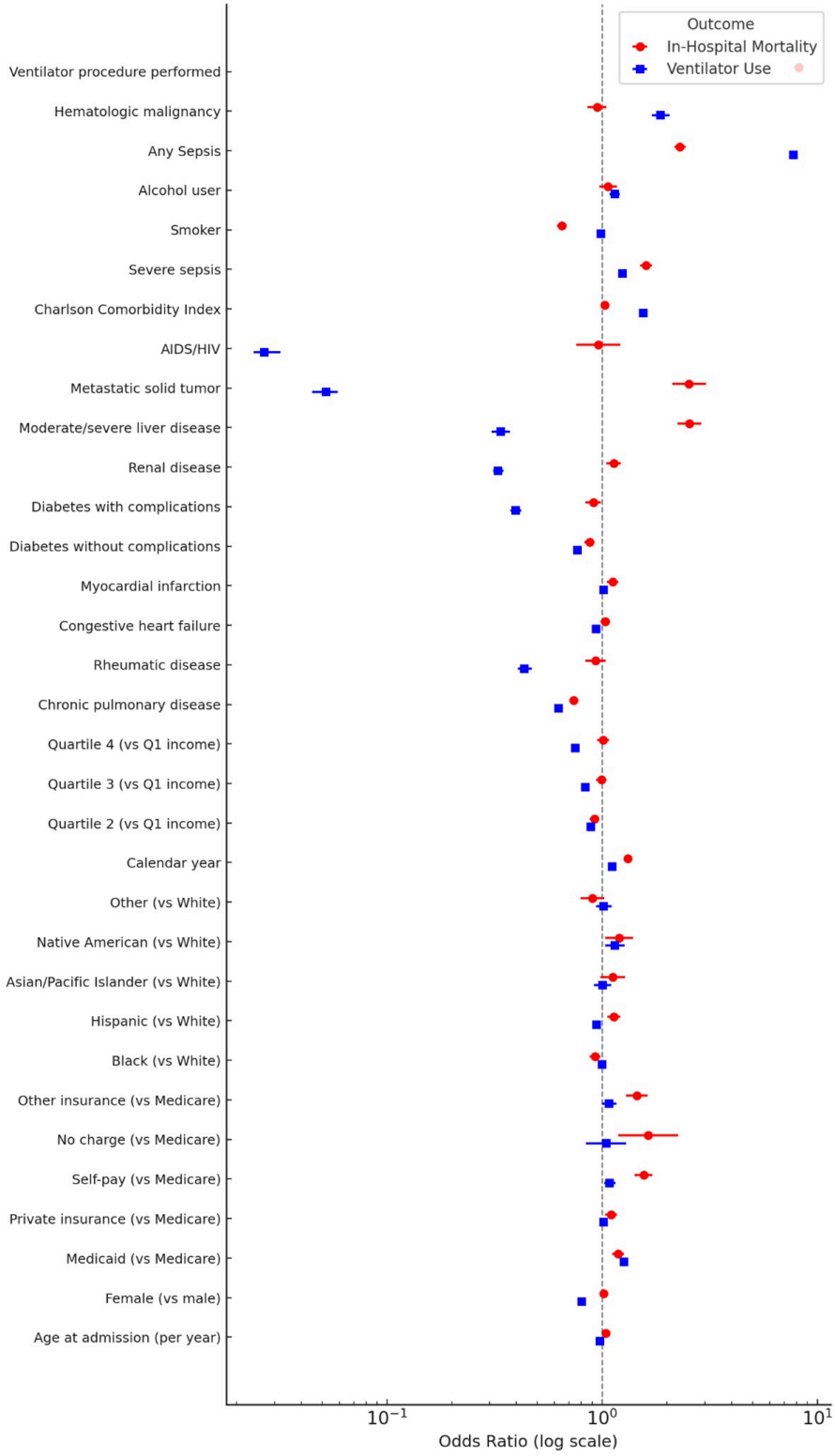


Figure 1

Forest Plots of Adjusted Odds Ratios for Ventilator Use and In-Hospital Mortality Among Hospitalized Patients With Hematologic Malignancy

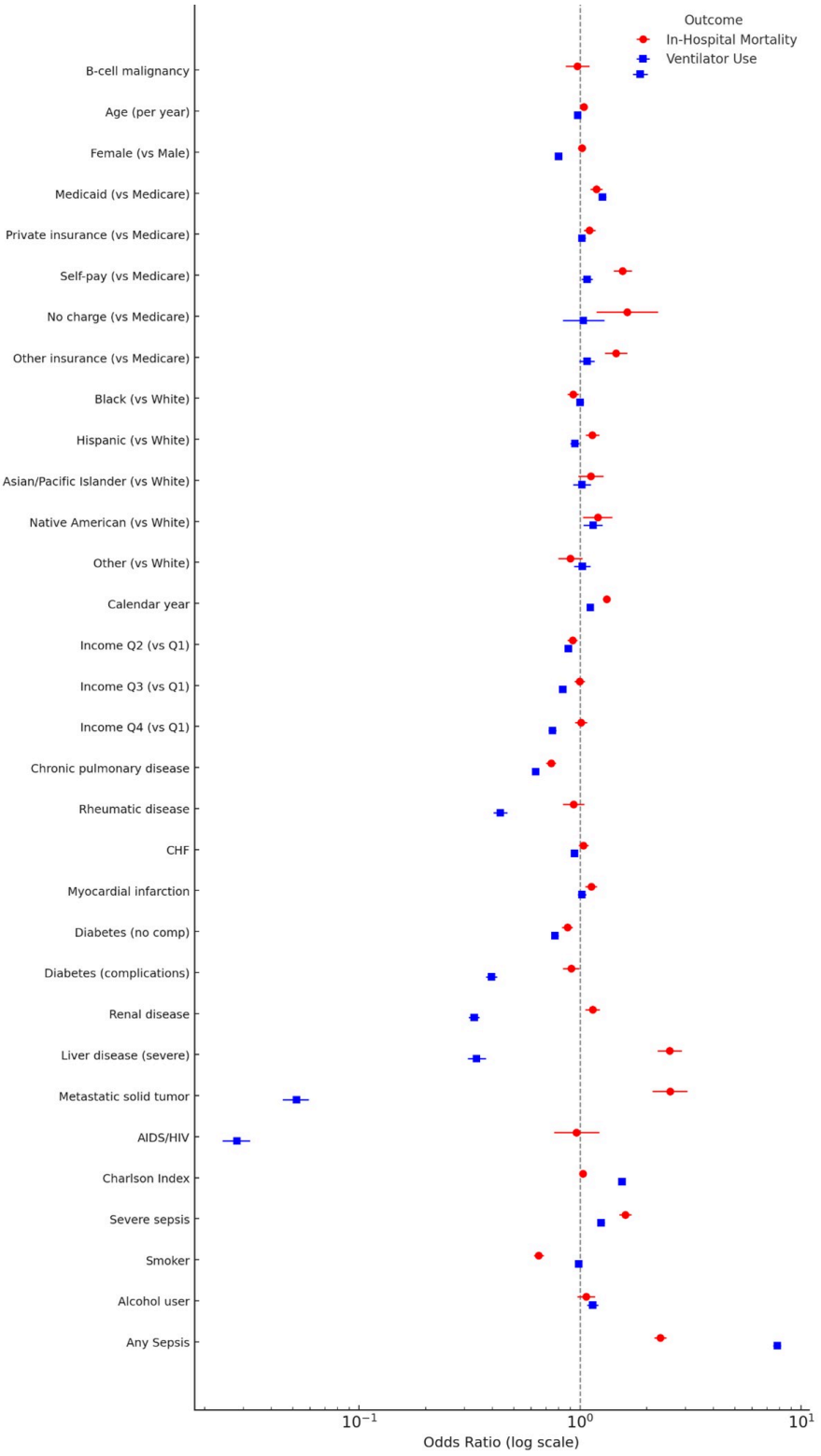


Figure 2

Adjusted Odds Ratios for Ventilator Use and In-Hospital Mortality Among Hospitalized Patients With B-Cell Hematologic Malignancy

Supplementary Files

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- SupplementaryTable1.docx