# Hospitalization Costs of Common Grade 3/4 Adverse Events Associated With Oncology Treatments in the United States

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## OBJECTIVES

- Grade 3/4 adverse events (AEs) are commonly observed in cancer treatment due to the nature of some cancer therapies and can be costly to treat and manage.
- The Common Terminology Criteria for Adverse Events standardizes the classification and severity of AEs in cancer therapy.[1] It provides the following general guidance:
  - Grade 3 AEs are "severe or medically significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicate; disabling; limiting self-care activities of daily living."
  - Grade 4 AEs are "life-threatening consequences; urgent intervention indicated."
- Many United States (US) cost-effectiveness and budget impact models for oncology treatments obtain grade 3/4 AE costs from HCUPnet, a public website query tool of the National Inpatient Sample (NIS) from the Healthcare Cost and Utilization Project (HCUP).[2]
- Recently, HCUPnet has shifted its policy by which users are allowed to identify hospitalization costs and length of stay (LOS): previously this information was accessed via detailed diagnosis codes (*International Classification of Diseases, Tenth Revision* [ICD-10]), but now users are only allowed access to broader categories not useful for parameterizing costs in economic models.
- We sought to estimate costs and LOS of commonly observed grade 3/4 AEs directly from survey data from the NIS of the HCUP using mapped ICD-10 codes.

## METHODS

### AE Identification

- The most commonly reported grade 3/4 AEs were identified from the prescribing information (PI) for all Food and Drug Administration (FDA)–approved novel therapies with an oncology indication in 2023 and 2024 as of 1 June 2024.
- Selected AEs were mapped to ICD-10 codes.

## Data Source

- HCUP consists of a variety of databases dating back to 1988, making the project the largest collection of longitudinal hospital data in the US.
- HCUP consists of 8 different databases, including the State Emergency Department Databases, the Kids' Inpatient Database (KID), and the NIS.
- The NIS is produced annually and is the largest publicly available inpatient healthcare database in the US.
- The NIS sample is designed to be nationally representative, representing over 97% of inpatient discharges from community hospitals in the US.
- Hospitalization cost and LOS data from all US payers is available in the NIS.
- Additional data allow for analysis of quality of health services, medical practice patterns, access to healthcare programs, and treatment outcomes.

## Data Analysis

- Survey and sampling design were accounted for by calculating weighted hospitalization costs and LOS for each code from the most recent NIS dataset available (2021) at the time of abstract submission using R.
- Means and standard errors are reported.
- HCUPnet warns users that "statistics based on estimates with a relative standard error (standard error/weighted estimate) greater than 0.30 or with standard error = 0 in the nationwide statistics (NIS, National Emergency Department Sample, and KID) are not reliable."
  - The same guidance was used to determine unreliable estimates in this analysis.

# RESULTS

All results are summarized in Table 1.

**Table 1. FDA-approved novel therapies for an oncology indication in 2023 and 2024**

| Name of drug | Indication | Approval date |
|---|---|---|
| Pirtobrutinib | To treat relapsed or refractory mantle cell lymphoma in adults who have had at least 2 lines of systemic therapy, including a Bruton tyrosine kinase inhibitor | 1/27/2023 |
| Elacestrant | To treat estrogen receptor–positive, human epidermal growth factor receptor 2-negative, ESR1-mutated, advanced or metastatic breast cancer with disease progression following at least 1 line of endocrine therapy | 1/27/2023 |

| Name of drug | Indication | Approval date |
|---|---|---|
| Retifanlimab-dlwr | To treat metastatic or recurrent locally advanced Merkel cell carcinoma | 3/22/2023 |
| Epcoritamab-bysp | To treat relapsed or refractory diffuse large B-cell lymphoma (not otherwise specified) and high-grade B-cell lymphoma after 2 or more lines of systemic therapy | 5/19/2023 |
| Glofitamab-gxbm | To treat diffuse large B-cell lymphoma, not otherwise specified, or large B-cell lymphoma arising from follicular lymphoma after 2 or more lines of systemic therapy | 6/15/2023 |
| Quizartinib | To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria | 7/20/2023 |
| Talquetamab-tgvs | To treat adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies | 8/9/2023 |
| Elranatamab-bcmm | To treat adults with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy | 8/14/2023 |
| Toripalimab-tpzi | To treat recurrent or metastatic nasopharyngeal carcinoma when used together with or following other therapies | 10/27/2023 |
| Fruquintinib | To treat refractory, metastatic colorectal cancer | 11/8/2023 |
| Repotrectinib | To treat ROS1-positive non–small-cell lung cancer | 11/15/2023 |
| Capivasertib | To treat breast cancer that meets certain disease criteria | 11/16/2023 |
| Tislelizumab-jsgr | To treat unresectable or metastatic esophageal squamous cell carcinoma | 3/13/2024 |
| Nogapendekin alfa inbakicept-pmln | To treat bladder cancer | 4/22/2024 |
| Tovorafenib | To treat relapsed or refractory pediatric low-grade glioma | 4/23/2024 |
| Tarlatamab-dlle | To treat extensive stage small-cell lung cancer | 5/16/2024 |

## AEs Reported

- 16 novel therapies were approved by the FDA in 2023 and 2024 (as of June 1) for oncology indications (Table 2).
  - 8 of the approved therapies were monoclonal antibodies, 6 were small molecule inhibitors, 1 was an antagonist of estrogen receptors, and 1 was an interleukin-15 receptor agonist.
  - 3 drugs were approved to treat forms of lymphoma (1 in mantle cell, 2 in large B-cell), 2 in multiple myeloma, 2 in breast cancer, 2 in lung cancer, and 1 each in Merkel cell carcinoma, acute myeloid leukemia, nasopharyngeal carcinoma,

colorectal cancer, bladder cancer, esophageal cancer, and pediatric low-grade glioma.

- Relapsed/refractory disease was included in the indication wording for 6 drugs; advanced, metastatic, or recurrent disease in 5 drugs; and line of therapy restrictions in 6 drugs.

**Table 2. ICD-10 Codes, Costs, and LOS for the Most Commonly Reported Grade 3/4 AEs**

| AE/term | PIs reporting | Mapped ICD-10 | | Costs, US $[a] | | LOS, days | |
|---|---|---|---|---|---|---|---|
| | | Code[b] | Description | Mean | SE | Mean | SE |
| Fatigue | 14 | R53.83 | Other fatigue | 9,653.64 | 652.17 | 4.03 | 0.30 |
| Edema | 4 | R60.9 | Edema, unspecified | 7,621.37 | 590.20 | 2.86 | 0.27 |
| Musculoskeletal pain | 13 | M79.10 | Myalgia, unspecified site | 8,804.54 | 716.49 | 3.60 | 0.35 |
| Abdominal pain | 6 | R10.84 | Generalized abdominal pain | 9,085.43 | 317.23 | 3.38 | 0.18 |
| Dyspnea | 5 | R06.00 | Dyspnea, unspecified | 8,570.27 | 338.91 | 2.52 | 0.11 |
| Pneumonia | 4 | J18.9 | Pneumonia, unspecified | 11,516.74 | 87.75 | 4.60 | 0.02 |
| Upper respiratory tract infections | 7 | J06.9 | Acute upper respiratory infection, unspecified | 6,692.83 | 242.64 | 2.28 | 0.05 |
| Hemorrhage | 5 | R58 | Hemorrhage | 25,251.19 | 1,510.77 | 5.36 | 0.38 |
| Hemoglobin decreased | 14 | D64.9 | Anemia, unspecified | 9,944.01 | 916.68 | 3.45 | 0.19 |
| Platelet count decreased | 11 | D69.6 | Thrombocytopenia, unspecified | 15,039.84 | 1,679.15 | 4.20 | 0.54 |
| Neutrophil count decreased | 11 | D70.9 | Neutropenia, unspecified | 16,288.74 | 879.91 | 5.01 | 0.12 |
| Lymphocyte count decreased | 14 | D72.819 | Decreased white blood cell count, unspecified | 10,349.89 | 1,247.73 | 3.74 | 0.59 |
| Creatinine increased | 11 | R94.4 | Abnormal results of kidney function studies | 8,431.26 | 1,699.75 | 1.80 | 0.44 |
| Calcium decreased | 6 | E83.51 | Hypocalcemia | 9,266.39 | 362.20 | 3.89 | 0.14 |
| AST increased | 12 | R74.01 | Elevation of levels of liver transaminase levels | 9,227.67 | 849.93 | 2.86 | 0.18 |
| Potassium decreased | 13 | E87.6 | Hypokalemia | 8,805.10 | 130.68 | 3.69 | 0.06 |

| AE/term | PIs reporting | Mapped ICD-10 | | Costs, US $[a] | | LOS, days | |
|---|---|---|---|---|---|---|---|
| | | Code[b] | Description | Mean | SE | Mean | SE |
| ALT increased | 13 | R74.01 | Elevation of levels of liver transaminase levels | 9,227.67 | 849.93 | 2.86 | 0.18 |
| Potassium increased | 4 | E87.5 | Hyperkalemia | 10,571.87 | 196.11 | 3.74 | 0.06 |
| Nausea | 8 | R11.0 | Nausea | 11,000.50 | 1,190.58 | 3.42 | 0.33 |
| Vomiting | 7 | R11.10 | Vomiting, unspecified | 8,807.23 | 707.50 | 3.36 | 0.29 |
| Decreased appetite | 9 | R63.0 | Anorexia | 12,606.14 | 1,562.88 | 6.07 | 0.77 |
| Headache | 5 | R51.9 | Headache, unspecified | 8,649.01 | 196.18 | 2.50 | 0.06 |
| Triglycerides increased | 4 | E78.1 | Pure hyperglyceridemia | 12,000.88 | 498.84 | 4.36 | 0.17 |
| Sodium decreased | 10 | E87.1 | Hypo-osmolality and hyponatremia | 9,557.66 | 99.21 | 4.07 | 0.04 |
| Rash | 8 | R21 | Rash and other nonspecific skin eruption | 6,738.12 | 389.79 | 2.96 | 0.17 |
| Leukocytes decreased | 9 | D72.819 | Decreased white blood cell count, unspecified | 10,349.89 | 1,247.73 | 3.74 | 0.59 |
| ALP increased | 7 | R74.8 | Abnormal levels of other serum enzymes | 9,448.86 | 1,120.90 | 3.15 | 0.28 |
| Cytokine release syndrome | 5 | D89.839 | CRS grade unspecified | 4,573.80 | 1,420.74 | 1.50 | 0.35 |
| Phosphate decreased | 6 | E83.39 | Other disorders of phosphorus metabolism | 9,924.51 | 1,012.45 | 3.97 | 0.41 |
| Diarrhea | 9 | R19.7 | Diarrhea, unspecified | 8,910.14 | 291.64 | 3.56 | 0.09 |
| Albumin decreased | 7 | R77.8 | Other specified abnormalities of plasma proteins | 8,082.40 | 369.67 | 2.54 | 0.18 |
| Magnesium decreased | 4 | E61.2 | Magnesium deficiency | 5,750.43 | 2,277.98 | 0.67 | 0.27 |
| Increased random glucose | 5 | R73.09 | Other abnormal glucose | 6,939.59 | 2,855.77 | 2.33 | 0.54 |

| AE/term | PIs reporting | Mapped ICD-10 | | Costs, US $[a] | | LOS, days | |
|---|---|---|---|---|---|---|---|
| | | Code[b] | Description | Mean | SE | Mean | SE |
| Increased fasting glucose | 5 | R73.01 | Impaired fasting glucose | 9,623.26 | 5,100.42 | 1.67 | 0.27 |
| Fever | 5 | R50.9 | Fever, unspecified | 9,387.65 | 191.55 | 3.18 | 0.04 |

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CRS = cytokine release syndrome; SE = standard error.

[a] Costs reported in 2021 US dollars.

[b] D89.839, E61.2, R73.09, and R73.01 are based on a small sample size (n = 2 for D89.839 and n = 3 for the others); therefore, cost estimates are not considered reliable. Additionally, LOS estimates are not considered reliable for E61.2.

- 35 total grade 3/4 AEs were reported across the 16 PIs.
  - 35 grade 3/4 AEs were reported in the PIs of ≥4 treatments and form the basis of our cost and LOS reporting.
  - Fatigue, decreased lymphocyte count, and decreased hemoglobin were the most reported AEs (14/16 PIs), followed by musculoskeletal pain, decreased potassium, and increased alanine aminotransaminase (13/16 PIs).
  - Increased aspartate transaminase was reported in 12/16 PIs, and decreased platelet count, decreased neutrophil count, and increased creatinine were reported in 11/16 PIs.

## Costs and LOS

- Of AEs with reliable estimates (i.e., adequate sample size), total hospitalization costs (2021 US $) ranged from $6,693 for upper respiratory tract infection to $25,251 for hemorrhage.
- Total hospitalization costs (2021 US $) ranged from $6,693 for upper respiratory tract infections to $25,251 for hemorrhage.
- Mean LOS (days) ranged from 1.50 for cytokine release syndrome to 6.07 for decreased appetite.
- Mean costs and LOS across the 35 AEs were $10,317 and 3.42 days, respectively.
- From 2020 to 2021, the cost of increased creatinine changed the most out of the 35 AEs, increasing 40% from $6,032 in 2020 to $8,431 in 2021. Musculoskeletal pain saw the largest change in LOS, increasing 34% from a mean of 2.68 days in 2020 to 3.60 days in 2021.
- Compared with 2020 data, costs and LOS increased for 63% and 69% of AEs, respectively.

# CONCLUSIONS

- Many oncology treatment–related AEs are common across recently approved therapies.
- Reports of costs and LOS may be useful for parameterizing future economic models, and costs should be updated to current US dollars using an appropriate inflation index.
- As more cancer therapies are approved and HCUP releases future NIS data, costs and LOS information should be updated.

# REFERENCES

1. US DHHS. 2017 November 27. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf.

2. HCUP NIS. 2021. www.hcup-us.ahrq.gov/nisoverview.jsp.