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

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BACKGROUND & OBJECTIVES

- Grade 3/4 adverse events (AEs) are commonly observed due to the nature of some cancer therapies and can be costly to treat and/or manage.

- The Common Terminology Criteria for Adverse Events standardizes the classification and severity of AEs in cancer therapy. It provides the following general guidance[1]:
  - Grade 3 AEs are "severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; 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 of oncology treatments source grade 3/4 AE costs from HCUPnet, a public query tool for the National Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project (HCUP).[2]

- Recently, HCUPnet has shifted from allowing users to identify hospitalization costs and length of stay (LOS) via detailed diagnosis codes (*International Statistical Classification of Diseases, Tenth Revision* [ICD-10]) to allowing only broader categories that are 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

Adverse Event 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 for an oncology indication in 2023.

- Selected AEs were mapped to ICD-10 codes.

Data Source

- HCUP consists of 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 Nationwide Emergency Department Sample (NEDS), 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, with NIS data representing more than 97% of inpatient discharges from community hospitals in the US.

- Hospitalization cost and LOS data from all US payers are 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

- Accounting for survey and sampling design, weighted hospitalization costs and LOS were calculated using R for each code from the most recent NIS dataset available (2020) at the time of abstract submission.

- Means and standard errors were 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, NEDS, and KID) are not reliable."
  - The same guidance was used in this analysis to determine unreliable estimates.

RESULTS

- All results are summarized in Table 1.

Table 1. ICD-10 Codes, Costs, and LOS for the Most Commonly Reported Grade 3/4 AEs

Adverse event/term	Mapped ICD-10			Costs, US $[a]		LOS, days	
	PIs reporting	Code	Description	Mean	SE	Mean	SE
Fatigue	11	R53.83	Other fatigue	10,049.31	983.15	4.29	0.34
Edema	4	R60.9	Edema, unspecified	7,855.66	659.31	3.26	0.32
Musculoskeletal pain	10	M79.10	Myalgia, unspecified site	7,729.00	709.19	2.68	0.25
Abdominal pain	5	R10.84	Generalized abdominal pain	8,865.52	458.12	3.26	0.21
Dyspnea	4	R06.00	Dyspnea, unspecified	7,166.34	304.64	2.47	0.19
Upper respiratory tract infections	5	J06.9	Acute upper respiratory infection, unspecified	7,386.01	275.65	2.72	0.07
Hemoglobin decreased	11	D64.9	Anemia, unspecified	8,367.32	144.93	3.10	0.05
Platelet count decreased	9	D69.6	Thrombocytopenia, unspecified	12,601.18	628.55	3.95	0.24
Neutrophil count decreased	10	D70.9	Neutropenia, unspecified	15,292.14	629.30	5.02	0.11
Lymphocyte count decreased	11	D72.819	Decreased white blood cell count, unspecified	10,157.63	1,289.90	3.51	0.30
Creatinine increased	8	R94.4	Abnormal results of kidney function studies	6,032.21	1,552.05	2.40	0.39
Calcium decreased	6	E83.51	Hypocalcemia	8,428.93	329.26	3.54	0.12
AST increased	9	R74.01	Elevation of levels of liver transaminase levels	9,489.34	1,050.12	3.18	0.34
Potassium decreased	10	E87.6	Hypokalemia	8,399.80	138.99	3.55	0.05
ALT increased	10	R74.01	Elevation of levels of liver transaminase levels	9,489.34	1,050.12	3.18	0.34
Nausea	6	R11.0	Nausea	9,636.71	1,345.26	2.67	0.24
Vomiting	5	R11.10	Vomiting, unspecified	7,133.70	371.24	3.00	0.21
Decreased appetite	7	R63.0	Anorexia	11,280.71	1,563.83	5.48	0.65
Headache	4	R51.9	Headache, unspecified	8,074.34	271.78	2.31	0.11
Triglycerides increased	4	E78.1	Pure hyperglyceridemia	12,490.92	549.66	4.34	0.19
Sodium decreased	7	E87.1	Hypo-osmolality and hyponatremia	8,888.03	92.13	3.83	0.03
Rash	6	R21	Rash and other nonspecific skin eruption	7,145.17	448.49	3.00	0.21
ALP increased	6	R74.8	Abnormal levels of other serum enzymes	7,493.14	498.26	2.59	0.25
CRS	4	D89.839[b]	CRS grade unspecified	9,7602.43	65,229.68	45.00	31.54
Phosphate decreased	4	E83.39	Other disorders of phosphorus metabolism	11,522.40	1,790.61	4.08	0.36
Diarrhea	7	R19.7	Diarrhea, unspecified	8,042.20	2,10.73	3.40	0.08
Albumin decreased	5	R77.8	Other specified abnormalities of plasma proteins	8,259.05	7,40.77	2.54	0.36
Increased random glucose	4	R73.9	Hyperglycemia, unspecified	9,065.57	899.92	3.05	0.34
Increased fasting glucose	4	R73.9	Hyperglycemia, unspecified	9,065.57	899.92	3.05	0.34

ALP = alkaline phosphatase; AST = aspartate transaminase; SE = standard error.

[a] Costs reported in 2020 US dollars.

[b] D89.839 is based on a small sample size (n = 3); therefore, cost and LOS estimates are not considered reliable.

Table 2. FDA Approved Novel Therapies for an Oncology Indication in 2023

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's tyrosine kinase inhibitor	27 Jan 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	27 Jan 2023
Retifanlimab-dlwr	To treat metastatic or recurrent locally advanced Merkel cell carcinoma	22 Mar 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	19 May 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	15 Jun 2023
Quizartinib	To use as part of a treatment regimen for newly diagnosed acute myeloid leukemia that meets certain criteria	20 Jul 2023
Talquetamab-tgvs	To treat adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies	9 Aug 2023
Elranatamab-bcmm	To treat adults with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy	14 Aug 2023
Toripalimab-tpzi	To treat recurrent or metastatic nasopharyngeal carcinoma when used with or following other therapies	27 Oct 2023
Fruquintinib	To treat refractory metastatic colorectal cancer	8 Nov 2023
Repotrectinib	To treat ROS1-positive non-small cell lung cancer	15 Nov 2023
Capivasertib	To treat breast cancer that meets certain disease criteria	16 Nov 2023

Adverse Events Reported

12 novel therapies were approved by the FDA in 2023 for oncology indications (Table 2).

- 6 of the approved therapies were monoclonal antibodies, 5 were small molecule inhibitors, and 1 was an antagonist of estrogen receptors.
- 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, and 1 each in Merkel cell carcinoma, acute myeloid leukemia, nasopharyngeal carcinoma, colorectal cancer, and non-small cell lung cancer.
- Relapsed/refractory disease was included in the indication wording for 5 drugs; advanced, metastatic, or recurrent disease was included in the indication wording for 4 drugs; and line of therapy restrictions were applied in 6 drugs.

29 total grade 3/4 AEs were commonly reported across the 12 PIs.

- 29 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 commonly reported (11/12), followed by musculoskeletal pain, decreased neutrophil count, decreased potassium, and increased alanine aminotransaminase (all 10/12).
- Decreased platelet count and increased aspartate transaminase were each reported in 9/12 PIs.

Costs and Length of Stay

$ Mean costs and LOS across the **29 AEs** were $9,264 and 3.69 days, respectively.

- Cytokine release syndrome (CRS) was the most expensive and had the longest LOS; however, sample size was too low for reliable estimates.
- Of AEs with reliable estimates, total hospitalization costs (2020 US $) ranged from $6,032 for increased creatinine to $15,292 for decreased neutrophil count.
- LOS ranged from 2.31 days for headache to 5.48 days for decreased appetite.

CONCLUSION

- Many AEs of oncology treatments are common across recent approvals.

- Costs and LOS reported may be useful in parameterizing future economic models where costs should be updated to current US dollars using the 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 Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. 27 Nov 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed 21 March 2024.
2. HCUP National Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). 2020. Agency for Healthcare Research and Quality, Rockville, MD. https://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed 22 March 2024.

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