



# Association and risk factors of healthcare-associated infection and burden of illness among chemotherapy-induced ulcerative mucositis patients

P. S. Satheeshkumar<sup>1,2</sup> · M. P. Mohan<sup>3</sup>

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## Abstract

**Objectives** To evaluate the association and risk factors of healthcare-associated infection (HAI) and burden of illness among chemotherapy-induced ulcerative mucositis (UM) patients.

**Methods** For this research, US National Inpatient Sample database 2017 was utilized to study UM patients. The association of healthcare-associated infection-related burden of illness among UM patients was assessed on the outcome—length of hospital stays (LOS), total charges, in-hospital mortality, and discharge disposition.

**Result** In 2017, there were 11,350 adult (> 18 years of age) UM patients, among them there were 415 (3.5%) HAI. After adjusting for patient and clinical characteristics, UM patients with HAI were most likely to have higher total charges and longer LOS (1.91; 95% CIs: 1.51–2.41;  $P < 0.001$ ; 1.84; 95% CIs: 1.53–2.21;  $P < 0.001$ ) than those without HAI. Further, mortality was not significantly different. UM patients with HAI were less likely to have higher burden of illness who were younger, females, those living in non-metropolitan or micropolitan counties, and those with lower co-morbidity score. Additionally, UM patients with HAI were more likely to discharge to skilled nursing facility (SNF), intermediate care facility (ICF), and another type of facility (ATF), (aOR = 2.58 (1.16–5.76),  $P = 0.02$ ), than they were to discharge to self-care or home care.

**Conclusion** UM patients with HAI were more likely to have higher burden of illness and more likely to discharged to the SNF, ICF, and ATF rather than to home or self-care.

## Clinical relevance

UM patients when associated with HAI have higher burden of illness; a tailored approach to oral care might prevent HAIs and burden of illness among UM.

## Introduction

Patients undergoing high-dose chemotherapy for solid and hematologic malignancies are anticipated to encounter the adverse events of the chemotherapy [1]. Severe oral

mucositis or ulcerative mucositis (UM) is a debilitating adverse event requiring complex management approaches affecting the quality of life of cancer patients [2]. In 2021, 1,898,160 new cancer cases and 608,570 cancer deaths are expected in the United States of America (USA) [3]. Among those receiving standard care chemotherapy as part of cancer management, it is expected that 40% of them encounter some form of oral mucositis [2]. And those receiving high-dose chemotherapy as part of a cancer treatment regimen are expected to face approximately 70% UM [4–6]. This challenging consequence for cancer patients often results in hospitalization for additional management of UM and associated complications [7]. Reduced oral intake, bleeding, severe pain, and secondary oral infections, in turn, exaggerate the burden of illness by an increased cost of care and length of hospital stay [8–12]. As known, debilitated patients, including patients with cancer, have a high

✉ P. S. Satheeshkumar  
Satheeshkumar\_PoolakkadSankaran@hms.harvard.edu;  
Satheesh.Sankaran@roswellpark.org

M. P. Mohan  
minu\_mohan@student.uml.edu

<sup>1</sup> Harvard Medical School, Boston, MA 02115, USA

<sup>2</sup> Department of Oral Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, USA

<sup>3</sup> Zuckerberg College of Health Sciences, University of Massachusetts, Lowell, MA 01854, USA

likelihood for increased length of stay, leading to hospital-associated complications comprising healthcare-associated infections (HAI) [11]. At present, association of healthcare-associated infection among UM patients is a gap in knowledge. Conversely, it is necessary to study UM as it leads to negative consequences [13]. Previous studies indicate UM patients are more predisposed to increased length of stay (LOS) and healthcare costs [14, 15]. Knowingly, UM patients are prone to systemic infections [16, 17]; the oral cavity is a pool of millions of organisms; increased entry of microorganism to the systemic circulation through mucosal wound among cancer patient undergoing chemotherapy is likely [18–20]. However, systemic infections such as HAI are not studied effectively among those encountering severe adverse events of cancer treatment, such as UM. This study utilized the National Inpatient Sample database to examine the association of the HAI and burden of illness (length of stay, total charges, and discharge disposition) and in-hospital mortality. Further, risk factors associated with HAI and the burden of illness among those encountering chemotherapy-induced UM were evaluated.

## Methods

### Study design and data source

This study was a cross-sectional inpatient database analysis of hospitalized chemotherapy-induced UM patients using discharge data from the 2017 National Inpatient Sample (NIS) database obtained from the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ) [21]. NIS 2017 is organized as 20% stratified sample of discharges to characterize 97% of all discharges of US inpatient hospital admissions excluding rehabilitation and long-term acute care hospitals. The NIS dataset comprises patient sociodemographic, comorbidity information, in-hospital outcomes, hospital characteristics, and hospitalization charges. As this analysis was based on publicly available de-identified and anonymous data, this study was exempted by the institutional IRB.

### Study population

This study included patients with chemotherapy-induced ulcerative mucositis in the year 2017. ICD10-CM codes were utilized to identify oral mucositis (ulcerative) due to antineoplastic therapy (K1231). ICD-10-CM billable codes were used to identify hospitalizations with HAI, mainly ventilator-associated pneumonia (VAP), central line-associated bloodstream infection (CLABSI), catheter-associated

urinary tract infection (CAUTI), and *Clostridium difficile* infection (CDI) (supplementary file 1).

### Study measurements

In the study, key independent variable was healthcare-associated infection. The study outcome variables were hospital LOS, total charges, in-hospital mortality, and discharge disposition. LOS was calculated by subtracting the admission date from the discharge date. Total charges included total charge of the health services (in USD)—it includes all hospital utilization fees charged by the hospital and eliminates physician's payments. The outcome, in-hospital mortality was defined as mortality that happened during hospitalization coded from discharge disposition of patient (alive or dead). Discharge disposition implies the disposition of the patient at discharge categorized as (1) routine-discharge to home/self-care; (2) short-term hospital; (3) skilled nursing facility, intermediate care, another type of facility; (4) home healthcare, (5) against medical device, and (6) discharge alive, destination unknown.

In the study, 2017 UM cohorts' covariates included were patient level and clinical level characteristics. Patient characteristics included in the study were age, sex (male or female), race (White, Black, Hispanic, Asian or Pacific Islander, Native American, or Other), primary payer (Medicare, Medicaid, private insurance, self-pay, no charge, or other), and median household income based on zip code (first to fourth quartile) and patient's location (urban/rural—using a six-category urban–rural classification scheme for US counties developed by the National Center for Health Statistics) [21]. Clinical characteristics included admission origin (transferred-in, not transferred), transfer type (indicator of a transfer out of the hospital), admission type (elective vs. non-elective; elective indicates whether patients were electively hospitalized), and Elixhauser Comorbidity Index which was used to categorize comorbidities. The Elixhauser Comorbidity Index variables are listed in the HCUP database [22].

### Statistical analysis

Descriptive statistics were used to describe patient and clinical characteristics stratified by UM patients with HAI and without HAI. To account for the complex sampling of the NIS, survey adjusted methods—survey-weighted generalized linear model (Svyglm)—were used to provide original valuations of US population's resulting output [23]. For the total charges and LOS, those were not normally distributed; hence, we log-transformed, and the geometric mean was presented [24]. A value of 0.0001 was imputed for LOS of 0 days to avoid negative log

values. A Svyglm was utilized to evaluate the association between HAI status and the outcomes—LOS, total charge, in-hospital mortality, and discharge disposition. Multivariable Svyglm was used to assess the risk factors associated with healthcare-associated infection and burden of illness among chemotherapy-induced ulcerative mucositis patients. The multivariable Svyglm models of LOS, total charges, in-hospital mortality, and discharge disposition were adjusted for the age, sex, payer type, patient location, race, elective, an indicator of a transfer into the hospital, median household income, and comorbidity score. For the in-hospital mortality and discharge dispositions models (binomial), we fitted a family referring quasibinomial to the Svyglm. All analyses were two-tailed and statistical significance was determined using  $P < 0.05$ . All statistical analyses were performed using R 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

In 2017, the NIS documented a total of 11,350 adult (> 18 years of age) chemotherapy-induced UM (weighted—original patient numbers) discharges from the 7,159,694 (unweighted numbers—20% of the total patients) patients. There were 415 (3.5%) of UM patients with HAI. CLABSI represented the highest accounting for 65.8% of the cases, whereas CDI infections were 30.7% of the cases, CAUTI were 2.6% of the cases, and VAP were 0.9% of the cases. Baseline patient and clinical characteristics are provided in Table 1. There was statistically significant difference between UM patients with and without HAI in terms of age, patient location, and according to transfer out to a different facility.

The geometric mean of the total charge among UM without HAI is 85878 USD, and those with UM with HAI is 170569 USD,  $P < 0.001$ . The adjusted multivariable regression analysis showed that the UM with HAI patients were more likely to have higher total charges (coefficient and confidence interval back transformed from log-transformation: 1.91; 95% CIs: 1.51–2.41;  $P < 0.001$ ) than UM patients without HAI. The geometric mean of the LOS among those with UM without HAI is 8.9 days, and for those with UM with HAI is 16.3 days,  $P < 0.001$ . The adjusted multivariable regression analysis showed that the UM with HAI were more likely to have longer LOS (coefficient and confidence interval back transformed from log-transformation: 1.84; 95% CIs: 1.53–2.21;  $P < 0.001$ ) than UM patients without HAI.

The number and percentage of the mortality among UM patients without HAI are 390 (3.4%), and those with UM with HAI are 20 (4.8%),  $P = 0.47$ . In the adjusted analysis, mortality was not significantly different among UM patients with and without HAI, and the adjusted odds ratio (aOR)

was 1.59; 95% CIs: 0.57–4.45;  $P = 0.37$ . For discharge dispositions, UM patients with and without HAI were significantly different ( $P < 0.001$ ). Approximately, 53% were transferred to the home or self-care, 15.7% to short-term nursing facility (SNF), intermediate care facility (ICF), and another type of facility (ATF); and 25.3% to home health-care, whereas this was 64.8%, 7.2%, and 23% among UM patients without HAI.

Table 2 provides the adjusted regression results for LOS, total charges, and in-hospital mortality. UM with HAI were more likely to have higher total charges and longer LOS. Factors associated with higher total charge among UM patients with HAI were being Hispanic race, having private insurance, elective admission, and those transferred in from different acute care hospitals, whereas females when compared to males, younger age group, those living in non-metropolitan or micropolitan counties, and having lower comorbidity score were less likely to have higher total charges. Factors associated with longer LOS among UM with HAI included elective admission, transferred in from a different acute care hospital, and those having lower elixir comorbidity score were less likely to have longer LOS. Factor associated with in-hospital mortality among UM patients with HAI were elixir comorbidity score.

Table 3 provides the adjusted regression results for discharge disposition. In the adjusted model, while placing discharge to home/self-care as a reference, those UM patients with HAI were more likely to be discharged to SNF, ICF, or ATF (aOR: 2.58 (1.16–5.76),  $P = 0.02$ ). Factors associated with discharge to SNF, ICF, or ATF among UM patients with HAI were age, females when compared to males, UM patients transferred in from a different acute care hospital and co-morbidity score. While placing home/self-care as reference, discharge to HHC, there was a non-significant difference between UM patients with and without HAI (aOR: 1.47; 95% CIs: 0.89–2.44;  $P = 0.14$ ). Factors associated with UM with HAI patients transfer to HHC patients were age, co-morbidity score, elective admission type, and those UM patients transferred in from different acute care hospital.

## Discussion

This study indicates that occurrence of at least 1 HAI among UM patients was associated with 1.91 times increase in total charges and 1.84 times increase in hospital LOS when compared to UM patients without HAI. Further, UM patients with HAI compared to without HAI were more likely to discharge to SNF, ICF, or ATF than were home or self-care. However, there was no difference in in-hospital mortality among UM patients with HAI when compared to the UM patients without HAI.

**Table 1** Baseline characteristics of the UM patients—with and without healthcare-associated infection

	UM patients without HAI	UM patients with HAI	<i>P</i> value
AGE (mean (SD))	11,350 (96.5%)	415 (3.5%)	
Sex (%)	57 (15.8)	52.9 (18.5)	0.04
Female	5870 (51.7)	225 (54.2)	0.64
RACE (%)			0.3
White	7605 (69.4)	280(72.7)	
Black	1210(11.0)	30 (7.8)	
Hispanic	1185(10.8)	40(10.4)	
Asian or Pacific Islander, Native American, and Other	955 (8.7)	35 (9.1)	
Median household income (based on current year)			0.78
0–25th percentile	2430(21.8)	85(21.0)	
26th to 50th percentile	2820(25.3)	115(28.4)	
51st to 75th percentile	2950(26.4)	115(28.4)	
76th to 100th percentile	2960(26.5)	90(22.2)	
Expected primary payer (%)			0.90
Medicare	4200 (37.1)	150 (36.1)	
Medicaid	1545 (13.6)	70 (16.9)	
Private insurance	4955 (43.8)	175 (42.2)	
Self-pay, no charge, and other	625 (5.5)	20 (4.8)	
Patient location: NCHS urban–rural code (%)			0.02
“Central” counties of metro areas of $\geq 1$ million population	3585 (31.7)	120(28.9)	
“Fringe” counties of metro areas of $\geq 1$ million population	2955(26.2)	80(19.3)	
Counties in metro areas of 250,000–999,999 population	2310(20.5)	90(21.7)	
Counties in metro areas of 50,000–249,999 population	985(8.7)	20(4.8)	
Micropolitan counties	860(7.6)	60(14.5)	
Not metropolitan or micropolitan counties	600(5.3)	45(10.8)	
Admission type (%)			0.39
Elective	3780.0 (33.3)	155.0 (37.3)	
Indicator of a transfer into the hospital (%)			0.50
Not transferred in	10,400(91.8)	375(90.4)	
Transferred in from a different acute care hospital	725(6.4)	25(6.0)	
Transferred in from another type of health facility	205(1.8)	15(3.6)	
Weighted Elixir score mean (SD))	18.8(13.3)	18.4(15.1)	0.81
Disposition of Patient (No, %)			<0.001
Discharge to home/self-care	7355(64.8)	220(53.0)	
Skilled nursing facility, intermediate care, another type of facility	815(7.2)	65(15.7)	
Home healthcare	2640.0 (23.3)	105(25.3)	
Length of stay (geometric mean)	8.9 days	16.3 days	<0.001
Total charge (geometric mean)	85,878 USD	170,569 USD (2.9)	<0.001
Died (No, %)	390(3.4)	20(4.8)	0.47

Abbreviations: *SD*, standard deviation; *NCHS*, National Center for Health Statistics; *UM*, chemotherapy-induced UM; *HAI*, healthcare-associated infection

Note: All frequencies and percentages are weighted

The cohort—chemotherapy-induced UM—comprised a heterogeneous cancer group receiving chemotherapy for both solid and hematologic patients. Hospitalized cancer patients have a high likelihood of infections due to their immunologic competence, which is further complicated

by comorbidities or chronic illness. Reports indicate that HAI are a serious concern in the cancer care, and there are no dissimilarities in encountering HAI when considering the solid and hematological malignancies [25]. However,

**Table 2** Factors associated with hospital charge, length of stay, and mortality

	Coefficient and 95% CIs (back transformed from log transformation)		Adjusted odds ratio (95% CIs), <i>P</i> value
	Total charge	Length of stay	
<b>Healthcare-associated infection</b>			
UM without HAI	Reference	Reference	Reference
UM with HAI	1.91(1.51–2.41), <i>P</i> <0.001	1.84 (1.53–2.21), <i>P</i> <0.001	1.59 (0.57–4.45), <i>P</i> =0.37
Age	0.99 (0.98–0.99), <i>P</i> =0.004	0.99 (0.99–1.00), <i>P</i> =0.14	1.02 (0.99–1.04), <i>P</i> =0.16
<b>Sex</b>			
Male	Reference	Reference	Reference
Female	0.86 (0.78–0.95), <i>P</i> =0.003	0.92 (0.84–1.0), <i>P</i> =0.08	0.76 (0.48–1.21), <i>P</i> =0.25
<b>Race (%)</b>			
White	Reference	Reference	Reference
Black	0.89 (0.75–1.07), <i>P</i> =0.23	1.00 (0.88–1.15), <i>P</i> =0.91	0.97 (0.39–2.29), <i>P</i> =0.89
Hispanic	1.31 (1.07–1.60), <i>P</i> =0.009	1.05 (0.89–1.25), <i>P</i> =0.57	1.46 (0.63–3.37), <i>P</i> =0.37
Asian or Pacific Islander, Native American, and Other	1.01 (0.77–1.33), <i>P</i> =0.94	0.96 (0.73–1.25), <i>P</i> =0.76	0.81(0.36–1.83), <i>P</i> =0.61
<b>Expected primary payer</b>			
Medicare	Reference	Reference	Reference
Medicaid	1.15 (0.94–1.42), <i>P</i> =0.15	1.04 (0.85– 1.31), <i>P</i> =0.61	0.97 (0.39– 2.38), <i>P</i> =0.94
Private insurance	1.15 (1.01–1.29), <i>P</i> =0.03	1.04 (0.93– 1.18), <i>P</i> =0.45	0.92 (0.48– 1.21), <i>P</i> =0.81
Self-pay, no charge, and Other	1.13 (0.86–1.49), <i>P</i> =0.38	1.12 (0.91–1.38), <i>P</i> =0.29	1.09 (0.29–4.02), <i>P</i> =0.89
<b>Patient Location: NCHS urban–rural code</b>			
Central counties of metro areas of ≥ 1 million population	Reference	Reference	Reference
Fringe counties of metro areas of ≥ 1 million population	0.89 (0.75–1.06), <i>P</i> =0.19	1.03 (0.90–1.17), <i>P</i> =0.66	0.96 (0.49–1.89), <i>P</i> =0.92
Counties in metro areas of 250,000–999,999 population	0.84 (0.70–0.99), <i>P</i> =0.05	0.98 (0.87–1.12), <i>P</i> =0.78	0.79 (0.39–1.60), <i>P</i> =0.52
Counties in metro areas of 50,000–249,999 population	0.81 (0.66–0.99), <i>P</i> =0.05	1.04 (0.88–1.22), <i>P</i> =0.65	1.08 (0.44–2.67), <i>P</i> =0.86
Micropolitan counties	0.85 (0.67–1.08), <i>P</i> =0.18	0.99 (0.76–1.27), <i>P</i> =0.91	1.61 (0.66–3.91), <i>P</i> =0.29
Not metropolitan or micropolitan counties	0.67 (0.52–0.85), <i>P</i> =0.001	0.79 (0.58–1.06), <i>P</i> =0.11	0.99 (0.31–3.19), <i>P</i> =0.99
Weighted Elixir score mean	0.99 (0.98–0.99), <i>P</i> =0.009	0.99 (0.98–.99), <i>P</i> =0.007	1.05 (1.04–1.07), <i>P</i> <0.001
<b>Admission type</b>			
Non-elective	Reference	Reference	Reference
Elective	2.33 (1.99–2.83), <i>P</i> <0.001	2.03 (1.81–2.28), <i>P</i> <0.001	0.51 (0.25–1.05), <i>P</i> =0.07
<b>Indicator of a transfer into the hospital</b>			
Not a transfer	Reference	Reference	Reference
Transferred in from a different acute care hospital	1.78 (1.43–2.22), <i>P</i> <0.001	1.94 (1.61– 2.36), <i>P</i> <0.001	0.71 (0.24– 2.07), <i>P</i> = 53
Transferred in from another type of health facility	0.93 (0.6–1.44). <i>P</i> =0.75	1.18 (0.85–1.67), <i>P</i> =0.32	1.38 (0.38–5.19), <i>P</i> =0.61
<b>Median household income based on patient's income</b>			
0–25th percentile	Reference	Reference	Reference
26th to 50th percentile	1.13 (0.98–1.31), <i>P</i> =0.09	1.08 (0.93–1.24), <i>P</i> =0.31	1.53 (0.72–3.26), <i>P</i> =0.27
51st to 75th percentile	1.13 (0.98–1.33), <i>P</i> =0.09	1.08 (0.93–1.25), <i>P</i> =0.32	1.48 (0.67–3.28), <i>P</i> =0.33
76th to 100th percentile	1.20 (0.99–1.45), <i>P</i> =0.05	1.07 (0.91–1.25), <i>P</i> =0.42	1.33 (0.58–3.08), <i>P</i> =0.49

Abbreviations: skilled nursing facility (SNF), intermediate care facility (ICF), and another type of facility, confidence intervals (CIs), odds ratio (OR). Healthcare-associated infection (HAI), ulcerative mucositis (UM)

**Table 3** Factors associated with discharge dispositions

Variables	Adjusted odds ratio (95% CIs), <i>P</i> value	
	Discharge disposition	
	SNF, ICF, and another type of facility) vs home/self-care	Home healthcare vs home/self-care
<b>Healthcare-associated infection status</b>		
UM without HAI	Reference	Reference
UM with HAI	2.58 (1.16–5.76), <i>P</i> =0.02	1.47 (0.89–2.44), <i>P</i> =0.14
Age	1.05 (1.03–1.08), <i>P</i> <0.001	1.01 (1.00–1.02), <i>P</i> =0.006
<b>Sex</b>		
Male	Reference	Reference
Female	1.08 (0.75–1.57), <i>P</i> =0.68	0.98 (0.79–1.24), <i>P</i> =0.89
<b>Race (%)</b>		
White	Reference	Reference
Black	1.07 (0.59–1.92), <i>P</i> =0.82	0.98 (0.72–1.33), <i>P</i> =0.89
Hispanic	0.49 (0.22–1.08), <i>P</i> =0.08	0.72 (0.49–1.04), <i>P</i> =0.08
Asian or Pacific Islander, Native American, and Other	0.96 (0.41–2.21), <i>P</i> =0.91	0.79 (0.41–1.51), <i>P</i> =0.48
<b>Expected primary payer</b>		
Medicare	Reference	Reference
Medicaid	1.06 (0.49–2.29), <i>P</i> =0.88	0.88 (0.57–1.35), <i>P</i> =0.56
Private insurance	0.59 (0.36–0.99), <i>P</i> =0.05	0.75 (0.56–1.00), <i>P</i> =0.05
Self-pay, no charge, Other	0.66 (0.22–1.95), <i>P</i> =0.45	0.45 (0.23–0.84), <i>P</i> =0.01
<b>Patient location: NCHS urban–rural code</b>		
Central counties of metro areas of ≥ 1 million population	Reference	Reference
Fringe counties of metro areas of ≥ 1 million population	1.03 (0.64–1.67), <i>P</i> =0.89	0.98 (0.73–1.31), <i>P</i> =0.87
Counties in metro areas of 250,000–999,999 population	1.25 (0.72–2.16), <i>P</i> =0.42	0.76 (0.54–1.08), <i>P</i> =0.13
Counties in metro areas of 50,000–249,999 population	0.83 (0.36–1.97), <i>P</i> =0.69	0.73 (0.47–1.14), <i>P</i> =0.17
Micropolitan counties	0.75 (0.34–1.66), <i>P</i> =0.48	0.77 (0.48–1.23), <i>P</i> =0.27
Not metropolitan or micropolitan counties	0.86 (0.34–2.21), <i>P</i> =0.76	0.60 (0.32–1.13), <i>P</i> =0.11
Weighted Elixir score mean	1.05 (1.04–1.06), <i>P</i> <0.001	1.02 (1.00–1.03), <i>P</i> =0.001
<b>Admission type</b>		
Non-elective	Reference	Reference
Elective	0.53 (0.31–0.89), <i>P</i> =0.02	1.45 (1.03–2.05), <i>P</i> =0.03
<b>Indicator of a transfer into the hospital</b>		
Not a transfer	Reference	Reference
Transferred in from a different acute care hospital	2.11 (1.12–3.99), <i>P</i> =0.02	1.99 (1.33–2.98), <i>P</i> =0.0009
Transferred in from another type of health facility	3.59 (0.87–14.88), <i>P</i> =0.08	1.48 (0.62–3.55), <i>P</i> =0.38
<b>Median household income based on patient's income</b>		
0–25th percentile	Reference	Reference
26th to 50th percentile	0.74 (0.43–1.29), <i>P</i> =0.29	0.83 (0.60–1.14), <i>P</i> =0.25
51st to 75th percentile	0.83 (0.46–1.48), <i>P</i> =0.52	1.00 (0.72–1.40), <i>P</i> =0.98
76th to 100th percentile	0.81 (0.43–1.53), <i>P</i> =0.52	1.01 (0.71–1.44), <i>P</i> =0.94

Abbreviations: skilled nursing facility (SNF), intermediate care facility (ICF), and another type of facility, confidence intervals (CIs), odds ratio (OR). Ulcerative mucositis (UM), healthcare-associated infection (HAI)

reports are highly elusive to determine the association of adverse events and HAI among cancer patients.

Expectedly, cancer patients have improved outcome due to better-quality and value-added available therapies; however, as these patients are critically ill, exposed to multiple treatments, and longer hospital days, consequently escalating

number of patients are exposed to the HAI [26]. The HAI are paramount concern among cancer patients as they are discharged to facilities for associated symptom management, involving acute care hospitals, ambulatory surgical centers, outpatient care, and long-term care facilities leading to higher financial burden [26–28]. While referring to

home or self-care, or post-acute care, patients are at risk of infections [26, 27]. HAIs are increasingly common in both developing and developed countries, burden associated with HAI are much higher, and charges associated managing these complications are extremely high. In the USA, the total annual costs for the five major HAIs (CLABSI, CAUTI, CDI, VAP, and surgical site infection) were USD 9.8 billion (95% CI, 8.3–11.5 billion USD) [28]. Exposure to these infections is fairly predictable in any hospitalized patients, as the risk increases with longer LOS and those are critically ill; identifying high-risk population is an achievable goal for any healthcare facility [28–32]. However, this is very different in the cancer care setting who seek care for infection and sepsis, as the predictability is less due to lack of scoring system and survival prediction [33, 34].

Risk of infection among UM patient may be multifactorial; patients receiving chemotherapy are at risk of neutropenia—a medical emergency if associated with fever (febrile neutropenia)—an early inflammatory response to a serious infection; oral complications of cancer treatment including mucositis might be a high-risk factor for neutropenia [35, 36]. A late response to infection or neutropenic patients unable to respond to systemic infection proceeds to rapidly progressive complications leading to systemic inflammatory response syndrome, sepsis, and septic shock. As explained by Zecha et al., there may be potential contribution by oral sources of infection and inflammation to progress to febrile neutropenia; a potential path of entry to systemic circulation is very likely through oral mucosal wounds, for which a conclusive evidence is still not available [36]. However, salivary gland dysfunction, dysregulation of oral microbiome, pre-existing oral condition, and periodontal disease might contribute to combination of favorable environment for infectious process like febrile neutropenia to progress. Nonetheless, a slow-grade locomotion of HAI causing organisms through mucosal wounds to systemic circulation is exceedingly possible [18–20, 37]. As patients undergoing treatment for UM are associated with mild state of neutropenia, and chronic illness, possibility of these HAI causing microorganism growth are manifold [18–20].

Even though there are conflicting arguments on predictors of mucositis, most studies report younger age as strong predictor [38]; nevertheless, along with age studies reported, BMI [39], smoking status [40, 41], neutropenia [42], lymphopenia [43], low hemoglobin levels [43], and renal dysfunction [44] are reported as risk factors. This study showed mean  $\pm$  age among UM patients with HAI of 53 years  $\pm$  18.5, and those without HAI of 57  $\pm$  15.8. Higher total charge was associated with UM patients with HAI who were Hispanic race, having private insurance, elective admission, and those transferred in from different acute care hospitals, whereas females when compared to males, younger age, those living in non-metropolitan/micropolitan counties, and having lower

comorbidity score were associated with a lower total charge among UM patients with HAI. Among UM patients with HAI, elective admission, and transferred in from different acute care facility were associated with longer LOS, whereas lower comorbidity score was associated with reduced LOS. Comparable to other oral mucositis studies [38, 44, 45], an insight to reflect are UM patients with HAI, who have lower comorbidities, females when compared to males, and young age, are less likely to have a high burden of illness. Conversely, it is known that a higher drug dose is predictably a risk factor for toxicities and related complications, [46] measuring those aspects are limited in the current study.

The post-acute care is an important driver of cost of care, and most Medicare beneficiaries require discharge to post-acute care [47–49]. This study noted UM patients with HAI are more likely to discharge to SNF, ICF, and ATF, than to home or self-care. Further, the study showed age, comorbidity score, and elective admission were associated with discharge to SNF, ICF, and ATF than home or self-care. Lately it has been reported that the burden of illness is reduced among those received comfort care from post-acute facilities [50]. Nevertheless, debilitated cancer patients are in need of post-acute care as most are associated with multitude of symptoms and post-acute care referral might benefit from receiving comfort care [51]. We also expect that UM patients with HAI might require symptom management and necessitate and long-term post-acute care. However, from this study, we may not be able to determine the burden of illness among those undergoing post-acute care at other facilities. Evaluating the radiation-induced mucositis and immunotherapy-induced oral mucositis correspondingly is an important issue to be tackled; we are unable to study those aspects due to the nature of the database and further due to the limitation to incorporate additional details in this manuscript.

Infection has been a concern among those undergoing high dose chemotherapy [18–20, 36, 52, 53]; a study on infectious complications among those undergoing high-dose chemotherapy for hematologic malignancy reported oral mucositis, and central venous catheter infection has been described to be a most common source of infection [54].

During this COVID-19 pandemic, a report suggests association of COVID-19 severity with duration of mucositis and pain [55]. Contemporary understanding of risk of infectious disease such as COVID-19 among those having severe adverse events of cancer therapy is very limited. This research showed UM patients when affected with HAI have a huge impact by increasing the hospital total charges, length of hospitalization stays, and discharged for care at other facility than self-care or home.

The study findings have many limitations. First, it is likely for one patient to be readmitted and counted more than once as the data is from discharge information. At one point of time, a patient can appear in HAI group and non-HAI group

at a different point. Second, our cohort was chemotherapy-induced UM patients (without the information of grades) who were treated for cure; being said that these are heterogeneous cancer patients having different cancer status and stage, we were unable to account for the effects of these variables in our analyses. Third, we estimated hospital charges rather than true cost; this may vary across hospital systems and also do not include all possible charges incurred such as administrative costs. Fourth, we used ICD-10-codes to identify UM consultation which may be subject to errors. Fifth, we have used the in-hospital mortality rather than the 30-day or 90-day mortality; such information's are available elsewhere. Additionally, the HAIs may be pretentious among radiation-induced UM and immunotherapy-induced UM, the data availability, and inclusion of those pieces are out of scope of this research; however, this research yields a platform how the burden of illness is modified among those with adverse events such as UM and HAI.

## Conclusion

This study showed that burden of illness (LOS, total charge, and discharge dispositions) among UM patients with HAI vs UM patients without HAI are different when covariates are accounted for. However, the in-hospital mortality was not different across the UM patients with and without HAI. UM patients with HAI were younger than UM patients without HAI. Further, higher comorbidity score, elective admission, and transferred in from different acute care hospitals were associated with higher burden of illness among UM with HAI. Utilizing a longitudinal evaluation of cancer treatment adverse events would be an ideal approach in understanding the association of HAI with UM stratified to different cancer cohorts and treatment regimen. As cancer patients are sick, predicting survival and clinical outcome among cancer patients undergoing treatment for infectious complications is tedious due to lack of risk scores. Moreover, the burden of illness associated with HAI among UM patients are compounded by patient and clinical characteristics.

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**Authors' contributions** Poolakkad S Satheeshkumar had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design:* Poolakkad S Satheeshkumar and Minu P Mohan. *Acquisition, analysis, or interpretation of data:* Poolakkad S Satheeshkumar and Minu P Mohan. *Drafting of the manuscript:* Poolakkad S Satheeshkumar

and Minu P Mohan. *Critical revision of the manuscript for important intellectual content:* Poolakkad S Satheeshkumar and Minu P Mohan. *Statistical analysis:* Poolakkad S Satheeshkumar, Minu P Mohan. *Supervision:* Poolakkad S Satheeshkumar and Minu P Mohan.

**Data availability** We used data from the 2017 NIS database obtained from Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality (AHRQ).

**Code availability** International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) provided in manuscript and in supplementary file 1 and cited in the text. All statistical analyses were performed using R, Version 3.5.1 (R foundation for statistical computing, Vienna, Austria).

## Declarations

**Ethics approval** “This study is a secondary analysis of publicly available de-identified and anonymous data that is considered exempt by the IRB”.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Conflict of interest** The authors declare that they have no conflict of interest.

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