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Postoperative Hyponatremia in the Oncologic Orthopedic Patient: Incidence, Risk factors, and Outcomes

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Abstract

Background: The purpose of this study is to determine the incidence of hyponatremia (serum [Na^+] <133 mEq/L) among cancer patients undergoing surgical procedures and characterize associated risk factors and outcomes.

Methods: This retrospective cohort analysis included adult surgical patients with a minimum of two hours of anesthesia time and post-surgical serum sodium level within 30 days in 2019. Univariable and multivariable logistic regression models were used to investigate associations between hyponatremia and 30-day all-cause mortality and Length of Stay (LOS). A subgroup analysis examined hip *vs*. knee procedures for orthopaedic oncology patients.

Results: 24,137 patients were included in our study; of which 1,445 patients had orthopaedic surgery. Postoperative hyponatremia was noted in 15% of orthopedic patients and 13.5% of other surgical patients. Postoperative hyponatremia (OR=2.58 [95% Confidence Interval (CI), 2.01–3.30], p<0.001) and orthopedic surgery (1.85 ([1.28-2.66], p=0.001) were independently associated with higher 30-day mortality. It was also associated with longer LOS [7.0 *vs*. 4.0; p<0.001]. Multivariable analysis showed a 32% increase in LOS for hyponatremia patients ([1.30-1.35], p<0.001) and 20% increase for the orthopaedic patients ([1.16-1.23], p<0.001). Subgroup analysis of orthopaedic procedures revealed a higher prevalence of postoperative hyponatremia in hip compared to knee procedures (21.5% *vs*. 11.4%, p=0.042). Multivariable analysis demonstrated a 27% increase in LOS among hyponatremic patients ([1.13-1.43], p<0.001).

Conclusion: Postoperative hyponatremia is associated with longer hospital stay and higher mortality in surgical oncology patients, and especially in orthopaedic procedures.

Keywords: Hyponatremia; Orthopedics; Oncology; Cancer; Outcomes; Postoperative

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Introduction

Hyponatremia is the most common electrolyte abnormality encountered in the hospital setting [1,2]. It is typically defined by serum sodium levels below 135 mEq/L. Hyponatremia can cause a myriad of symptoms including nausea, headache, confusion, fatigue, irritability, spasms, seizures, and coma. Hyponatremia is directly associated with higher mortality and morbidity [1,3-5]. Even mild hyponatremia can lead to higher mortality [4]. Appropriate and optimal treatment of hyponatremia can lead to improved quality of life for patients, and avoidance of these complications [6].

Causes of hyponatremia are generally due to retention of water, impairment of renal excretion of water, or increased intake of water; the most common causes of hyponatremia include Syndrome of Inappropriate Antidiuretic Hormone (SIADH), polydipsia, hyperglycemia, diuretic use, adrenal insufficiency, cirrhosis, and heart failure [5,7]. The risk of hyponatremia increases during hospital admissions and especially for perioperative patients [3,4].

Although hyponatremia tends to be mild or asymptomatic, there is a growing body of literature that suggests hyponatremia is associated with increased risk of adverse outcomes including increased length of stay (64% increase), discharge to a facility (adjusted odds ratio of 1.64), and

mortality (adjusted odds ratio of 1.66) [3,4]. The risk of mortality increases regardless of the severity of hyponatremia, and extends from inpatients through 5 years follow up [3]. There is a strong association between hyponatremia and mortality for patients with cardiovascular diseases and procedures, metastatic diseases, and postoperative orthopedic procedures [8-10]. The effects of hyponatremia include worse outcomes and increased economic burden on the healthcare system [11-13].

Orthopedic surgical procedures carry high risk of postoperative hyponatremia and several studies estimate the prevalence of postoperative hyponatremia after orthopedic procedures between 30% to as high as 84.9% [14-16]. Specifically, patients undergoing spine fusions, hip fracture repairs, total hip arthroplasties and total knee arthroplasties are at an increased risk of developing postoperative hyponatremia; these patients hospital course included longer hospital stays, higher complications rates, and greater mortality [16-18]. One study reported that postoperative hyponatremia in orthopedic patients resulted in an overall increase of $1800 in hospital cost, 2.87 odds of being discharged to an extended-care facility, and longer hospital stay [9]. Similarly, metastatic disease is associated with higher risk of developing hyponatremia, longer hospital stays, and higher mortality. In a study analyzing head and neck squamous cell carcinoma in head and neck patients, the prevalence of hyponatremia was 31.9% with higher perioperative morbidities [19]. Another study found the prevalence of hyponatremia to be 47% for cancer patients, with increased hazard ratios for length of stay and 90-day mortality that correlated with higher severity of hyponatremia [8].

Orthopedic procedures are among the most common surgical procedures in the oncologic setting. Despite the high prevalence of these procedures, the association of hyponatremia on patient outcomes has not been investigated. We seek to determine the prevalence, risk factors, and outcomes of hyponatremia in this population.

Material and Methods

We retrospectively reviewed the electronic medical charts of all adult (≥ 18 years old) hospitalized patients undergoing surgical procedures that required a minimum of 2 h of anesthesia time at a tertiary academic cancer medical center from January to December, 2019. Inclusion criteria included inpatient or same day hospitalization patients in surgical services, ≥ 18 years old, minimum 2 h of anesthesia time, and a minimum of one post-surgical sodium and glucose lab value within 30 days. Exclusion criteria included <18-year-old patients. Hyponatremia was defined as a corrected sodium level <133 mEq/L (correction for sodium level with glucose was made with the following calculation: Corrected sodium = measured sodium *0.024* (serum glucose -100)). Corrected sodium was utilized because hyperglycemia can create a translocational hyponatremia, which results in a shift of water from cells to the extracellular fluid compartment [5,20,21].

The study has been approved by the IRB at MSKCC, and the study is performed in accordance with the ethical standards in the 1964 Declaration of Helsinki. The request to waive the requirement to obtain written informed consent and a research authorization has been granted as per 45 CFR 46.116(c) (d) and 45 CFR 164.512(i) (1) (ii) by the MSKCC IRB.

Data collection

Sodium levels were analyzed up to thirty days post-operatively. Data on patients included demographics, medications, and comorbidities listed in the Elixhauser comorbidity index. Anesthesia records were reviewed for intraoperative variables. Hospital length of stay (including ICU stay), thirty-day all-cause mortality, and complications were documented.

Outcomes

Our primary outcome was the prevalence of hyponatremia in the orthopedic surgery cohort and all other surgical services. Secondary outcomes explored the differences between the orthopedic group and all other surgeries, as well as intraoperative differences (hip *vs.* knee procedures) within the orthopedic cohort in terms of hospital length of stay and thirty-day all-cause mortality.

Statistical analysis

Median and Interquartile Range (IQR), 25th and 75th percentiles were used for continuous variables and groups were compared using Wilcoxon rank sum test. Count and percentage were presented for categorical variables and groups were compared using Chi-square test. Hyponatremia was defined as a patient having any post-surgical sodium level below 133 within 30 days of surgery. Univariable and multivariable logistic regression and linear regression models were used to assess associations with secondary outcomes of 30-day mortality and Length of Stay (LOS). A sub- group analysis was done on a group of patients who had hip or knee orthopedic surgery. Backward selection was used for multivariable analysis and a factor was entered if $p<0.1$ in the univariable analysis. SAS version 9.4 SAS institute Inc., Cary, NC was used for all analysis. All tests were two-sided and $p<0.05$ was considered significant.

Results

Demographics

A total of 24,974 adult patients that underwent surgery between January 2019 to December 2019 with anesthesia duration of at least two hours were evaluated for inclusion. After excluding patients without post-surgical sodium and/or glucose laboratory results, 24,137 were included in the final analysis. Median age of the patient was sixty-two years (IQR: 51-71). A majority of patients were female (n=13,039, 54.02%), white (n=19,071, 81.32%) and 8.26% were Asian (n=1938), 6.96% were black (n=1632), and 3.46% were "other" (n=811). The median BMI was 27 (IQR: 23.5-31.1). The most frequent comorbidity reported was hypertension (n=9598, 39.76%) and the most common medication was NSAID (n=13868, 57.46%). Table 1 lists demographic details of the study population as a whole and by

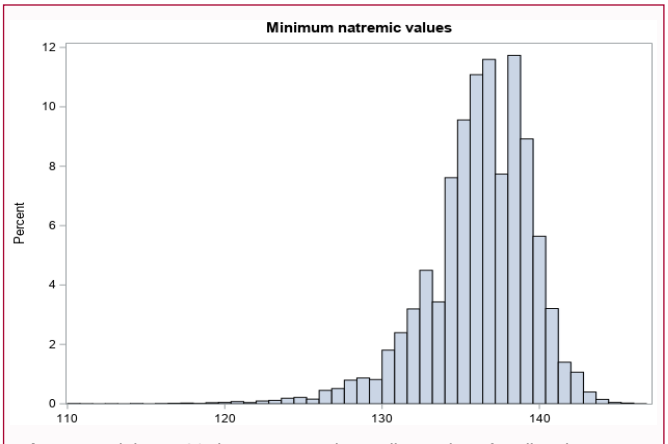

Figure 1: Minimum 30-day postoperative sodium values for all patients.

Table 1: Prevalence, characteristics, and risk factors for postoperative hyponatremia.

	Normonatremic (N=20859)	Hyponatremic (N=3278)	Total (N=24137)	P Value
Service				
Ortho	1228 (5.89%)	217 (6.62%)	1445 (5.99%)	0.100
Other	19631 (94.11%)	3061 (93.38%)	22692 (94.01%)	
Missing	0	0	0	
Age				
Median (IQR)	61.0 (51.0 -70.0)	66.0 (57.0-74.0)	62.0 (51.0-71.0)	<0.001
Range	18.00-98.00	19.00-95.00	18.00-98.00	
Sex				
F	11339 (54.36%)	1700 (51.86%)	13039 (54.02%)	0.008
M	9520 (45.64%)	1578 (48.14%)	11098 (45.98%)	
BMI				
Median (IQR)	27.2 (23.7-31.4)	25.5 (22.4-29.4)	27.0 (23.5-31.1)	<0.001
Range	12.20-109.00	13.50-67.30	12.20-109.00	
Race				
Asian	1623 (08.01%)	315 (09.87%)	1938 (08.26%)	<0.001
black	1476 (07.28%)	156 (04.89%)	1632 (06.96%)	
other	718 (03.54%)	93 (02.91%)	811 (03.46%)	
white	16444 (81.16%)	2627 (82.33%)	19071 (81.32%)	
Missing	598	87	685	
ANES_ASA_PS				
P1	81 (00.39%)	8 (00.24%)	89 (00.37%)	
P2	4419 (21.19%)	316 (09.64%)	4735 (19.62%)	
P3	15203 (72.88%)	2556 (77.97%)	17759 (73.58%)	
P4	1145 (05.49%)	390 (11.90%)	1535 (06.36%)	
P5	11 (00.05%)	8 (00.24%)	19 (00.08%)	
Missing	0	0	0	
ASA				
1,2	4500 (21.57%)	324 (09.88%)	4824 (19.99%)	
3	15203 (72.88%)	2556 (77.97%)	17759 (73.58%)	<0.001
4,5	1156 (05.54%)	398 (12.14%)	1554 (06.44%)	
Missing	0	0	0	
Elixhauser Score				
Median (IQR)	12.0 (4.0-12.0)	12.0 (9.0-17.0)	12.0 (4.0-14.0)	
Range	0.00-55.00	0.00-48.00	0.00-55.00	<0.001
Congestive Heart Disease				
N	20252 (97.09%)	3121 (95.21%)	23373 (96.83%)	
Y	607 (02.91%)	157 (04.79%)	764 (03.17%)	<0.001
Valvular Disease				
N	20041 (96.08%)	3075 (93.81%)	23116 (95.77%)	
Y	818 (03.92%)	203 (06.19%)	1021 (04.23%)	<0.001
Pulmonary Circulation Disorders				
N	20538 (98.46%)	3169 (96.67%)	23707 (98.22%)	
Y	321 (01.54%)	109 (03.33%)	430 (01.78%)	<0.001
Chronic Pulmonary Disease				
N	17619 (84.47%)	2640 (80.54%)	20259 (83.93%)	
Y	3240 (15.53%)	638 (19.46%)	3878 (16.07%)	<0.001

Peripheral Vascular Disease				
N	20138 (96.54%)	03107 (94.78%)	23245 (96.30%)	
Y	721 (03.46%)	171 (05.22%)	892 (03.70%)	<0.001
Hypertension				
N	12775 (61.24%)	1764 (53.81%)	14539 (60.24%)	
Y	8084 (38.76%)	1514 (46.19%)	9598 (39.76%)	<0.001
Hypertension Complications				
N	19331 (92.67%)	2886 (88.04%)	22217 (92.05%)	
Y	1528 (07.33%)	392 (11.96%)	1920 (07.95%)	<0.001
Diabetes				
N	18809 (90.17%)	2930 (89.38%)	21739 (90.07%)	
Y	2050 (09.83%)	348 (10.62%)	2398 (09.93%)	0.161
Diabetes Complications				
N	19999 (95.88%)	3112 (94.94%)	23111 (95.75%)	
Y	860 (04.12%)	166 (05.06%)	1026 (04.25%)	0.013
Renal Failure				
N	19597 (93.95%)	02989 (91.18%)	22586 (93.57%)	<0.001
Liver Failure				
N	19875 (95.28%)	3081 (93.99%)	22956 (95.11%)	0.001
Y	984 (04.72%)	197 (06.01%)	1181 (04.89%)	
Atrial Fibrillation or Flutter				
N	19648 (94.19%)	2990 (91.21%)	22638 (93.79%)	<0.001
Y	1211 (05.81%)	288 (08.79%)	1499 (06.21%)	
ESRD				
N	20771 (99.58%)	3242 (98.90%)	24013 (99.49%)	<0.001
Y	88 (00.42%)	36 (01.10%)	124 (00.51%)	
Coronary Stent				
N	20026 (96.01%)	3114 (95.00%)	23140 (95.87%)	0.007
Y	833 (03.99%)	164 (05.00%)	997 (04.13%)	

Table 2: Hospital and surgery characteristics and postoperative hyponatremic status.

	Normonatremic (N=20859)	Hyponatremic (N=3278)	Total (N=24137)	P Value
Anesthesia Minutes				
Median (IQR)	267.0 (202.0-368.0)	276.0 (205.0-368.0)	268.0 (202.0-368.0)	0.098
Range	120.00-1698.00	120.00-1222.00	120.00-1698.00	
Surgery Minutes				
Median (IQR)	191.0 (127.0-286.0)	197.0 (128.0-287.0)	192.0 (128.0-286.0)	0.322
Range	5.00-1607.00	0.00-1160.00	0.00-1607.00	
Anesthesia Type				
GEN	20859 (100.00%)	3278 (100.00%)	24137 (100.00%)	
Estimated Blood Loss				
Median (IQR)	100.0 (25.0-250.0)	150.0 (50.0-400.0)	100.0 (25.0-300.0)	<0.001
Range	0.00-15150.00	0.00-8070.00	0.00-15150.00	
30-Day Mortality				
N	20655 (99.02%)	3125 (95.33%)	23780 (98.52%)	<0.001
Y	00204 (0.98%)	153 (4.67%)	357 (1.48%)	
Length of Stay				
Median (IQR)	4.0 (2.0-7.0)	7.0 (4.0-13.0)	4.0 (3.0-7.0)	<0.001

Range	0.00-371.00	0.00-275.00	0.00-371.00	
ICU Stay				
N	20254 (97.10%)	2965 (90.45%)	23219 (96.20%)	<0.001
Y	605 (2.90%)	313 (9.55%)	918 (3.80%)	
In-Hospital Thiazide Drugs				
N	20021 (95.98%)	3083 (94.05%)	23104 (95.72%)	<0.001
Y	838 (4.02%)	195 (5.95%)	1033 (4.28%)	
In-Hospital Potassium Sparing Diuretics				
N	20651 (99.00%)	3167 (96.61%)	23818 (98.68%)	<0.001
Y	208 (1.00%)	111 (3.39%)	319 (1.32%)	
In-Hospital NSAIDS				
N	8845 (42.40%)	1424 (43.44%)	10269 (42.54%)	0.264
Y	12014 (57.60%)	1854 (56.56%)	13868 (57.46%)	
In-Hospital Beta Blockers				
N	15255 (73.13%)	2030 (61.93%)	17285 (71.61%)	<0.001
Y	5604 (26.87%)	1248 (38.07%)	6852 (28.39%)	
Postoperative Complication: Pulmonary				
N	19208 (92.08%)	2656 (81.03%)	21864 (90.58%)	<0.001
Y	1651 (7.92%)	622 (18.97%)	2273 (9.42%)	
Postoperative Complication: Stroke				
N	20825 (099.84%)	3258 (99.39%)	24083 (99.78%)	<0.001
Y	34 (0.16%)	20 (0.61%)	54 (0.22%)	
Postoperative Complication: Cardiac				
N	20643 (098.96%)	3192 (97.38%)	23835 (98.75%)	<0.001
Y	216 (1.04%)	86 (2.62%)	302 (1.25%)	
Postoperative Complication: Thrombosis				
N	20582 (98.67%)	3151 (96.13%)	23733 (98.33%)	<0.001
Y	277 (1.33%)	127 (3.87%)	404 (1.67%)	
Postoperative Complication: Pulmonary Embolism				
N	20752 (99.49%)	3224 (98.35%)	23976 (99.33%)	<0.001
Y	107 (0.51%)	54 (1.65%)	161 (0.67%)	
Postoperative Complication: Atrial Fibrillation/Flutter				
N	20471 (098.14%)	3127 (95.39%)	23598 (97.77%)	<0.001
Y	388 (1.86%)	151 (4.61%)	539 (2.23%)	
Postoperative Complication: Sepsis				
N	20680 (99.14%)	3150 (96.10%)	23830 (98.73%)	<0.001
Y	179 (0.86%)	128 (3.90%)	307 (1.27%)	

groups based on postoperative hyponatremia status.

Prevalence, risk factors, and associations

In total, 3278 (13.6%) of all surgical patients had postoperative hyponatremia (Figure 1). Within the orthopedic surgery cohort, only 15% of patients had post-operative hyponatremia, while 13.5% of patients in all other surgeries had post-operative hyponatremia. However, the difference between the orthopedic cohort and all other surgical services was not statistically significant (p=0.100).

Several risk factors were identified that were associated with higher risk of postoperative hyponatremia. Patients who developed hyponatremia were on average older compared to those who were normonatremic (median = 66 *vs.* 61 years, p<0.001). Male gender was associated with higher rate of hyponatremia than female gender (48.4% *vs.* 45.6%, p=0.008). Patients who self-identified race as white reflected higher rates of hyponatremia than their non-white counterparts. (White = 82.33%, Asian = 9.87%, Black = 4.89%, other = 2.91%; p<0.001). Surgery time and anesthesia time were not significantly associated with higher rates of hyponatremia, but higher estimated blood loss was significantly associated with developing hyponatremia (100 mL *vs.* 150 mL; p<0.001) (Table 2). Thiazides (5.95% *vs.* 4.02%, p<0.001), potassium sparing diuretics (3.39% *vs.* 1.00%; p<0.001), and beta-blockers (38.07% *vs.* 26.87%; p<0.001) were also significantly associated with hyponatremia. NSAID usage was not a significant risk factor (56.56% *vs.* 57.60%; p=0.264) (Table 2). Finally, all comorbidities with the exception of diabetes mellitus

Table 3: Univariate and multivariate analysis for length of stay.

	Univariate analysis		Multivariate analysis	
	exp Estimate (95% CI)	**p-value**	**exp Estimate (95% CI)**	**p-value**
Postoperative Hyponatremia				
Hyponatremic	1.65 (1.61-1.70)	<0.001	1.32 (1.30-1.35)	<0.001
Normatremic	Ref			
Service				
Ortho	1.30 (1.25-1.35)	<0.001	1.20 (1.16-1.23)	<0.001
Other	Ref			
Age	1.005 (1.004-1.005)	<0.001	0.999 (0.999-1.000)	0.024
Sex				
M	1.08 (1.06-1.10)	<0.001		
F	Ref			
BMI	0.99 (0.99-0.99)	<0.001	0.99 (0.99-0.99)	<0.001
Race				
Asian	1.03 (1.00-1.06)	0.071	1.01 (0.98-1.04)	0.434
Black	1.10 (1.06-1.14)	<0.001	1.10 (1.07-1.13)	<0.001
Other	1.00 (0.95-1.05)	>0.95	1.02 (0.98-1.06)	0.244
White	Ref			
ASA				
3	1.30 (1.28-1.33)	<0.001	1.16 (1.14-1.18)	<0.001
4,5	2.56 (2.47-2.66)	<0.001	1.64 (1.58-1.70)	<0.001
1,2	ref			
Elixhauser Score	1.03 (1.03-1.03)	<0.001	1.02 (1.02-1.02)	<0.001
Congestive Heart Disease				
Y	1.41 (1.35-1.49)	<0.001	0.84 (0.80-0.88)	<0.001
N	Ref			
Valvular Disease				
Y	1.23 (1.19-1.29)	<0.001		
N	Ref			
Pulmonary Circulatory Disorders				
Y	1.85 (1.73-1.98)	<0.001	1.10 (1.04-1.16)	<0.001
N	Ref			
Chronic Pulmonary Disease				
Y	1.05 (1.03-1.08)	<0.001	1.05 (1.03-1.08)	<0.001
N	Ref			
Peripheral Vascular Disease				
Y	1.26 (1.20-1.32)	<0.001		
N	Ref			
Hypertension				
Y	1.06 (1.04-1.08)	<0.001		
N	Ref			
Hypertension Complications				
Y	1.35 (1.31-1.40)	<0.001		
N	Ref			
Diabetes Mellitus				
Y	1.01 (0.98-1.04)	0.599		
N	Ref			

Diabetes Mellitus Complications				
Y	1.42 (1.36-1.48)	<0.001	1.15 (1.11-1.19)	<0.001
N	Ref			
Renal Failure				
Y	1.30 (1.26-1.35)	<0.001	0.96 (0.93-0.99)	0.014
N	Ref			
Liver Disease				
Y	1.22 (1.17-1.27)	<0.001	0.93 (0.90-0.96)	<0.001
N	Ref			
Atrial Fibrillation/Flutter				
Y	1.33 (1.28-1.37)	<0.001		
N	Ref			
ESRD				
Y	1.60 (1.41-1.80)	<0.001	0.76 (0.68-0.84)	<0.001
N	Ref			
Coronary Stent				
Y	1.13 (1.08-1.18)	<0.001	0.93 (0.89-0.96)	<0.001
N	Ref			
Anesthesia Hours	1.08 (1.07-1.08)	<0.001	1.07 (1.06-1.07)	<0.001
Surgery Hours	1.08 (1.07-1.08)	<0.001		<0.001
Estimated Blood Loss	1.04 (1.03-1.04)	<0.001	1.01 (1.01-1.01)	<0.001
ICU Stay				
Y	3.38 (3.24-3.53)	<0.001	1.52 (1.45-1.59)	<0.001
N	Ref			
In-Hospital Thiazide Drugs				
Y	1.15 (1.10-1.20)	<0.001	1.04 (1.00-1.07)	0.046
N	Ref			
In-Hospital Potassium Sparing Drugs				
Y	1,71 (1.58-1.84)	<0.001	1.30 (1.22-1.38)	<0.001
N	Ref			
In-Hospital NSAID				
Y	0.94 (0.92-0.96)	<0.001	1.02 (1.00-1.03)	0.023
N	Ref			
In-Hospital Beta Blocker				
Y	1.34 (1.32-1.37)	<0.001	1.10 (1.09-1.12)	<0.001
N	Ref			
Postop Complications: Pulmonary				
Y	2.19 (2.13-2.26)	<0.001	1.40 (1.36-1.44)	<0.001
N	Ref			
Postop Complications: Stroke				
Y	2.58 (2.14-3.10)	<0.001	1.23 (1.06-1.43)	0.007
N	Ref			
Postop Complications: Cardiac				
Y	2.10 (1.94-2.27)	<0.001		
N	Ref			
Postop Complications: Thrombosis				
Y	3.61 (3.38-3.85)	<0.001	1.79 (1.70-1.90)	<0.001
N	Ref			

Postop Complications: Pulmonary Embolism				
Y	3.22 (2.90-3.58)	<0.001		
N	Ref			
Postop Complications: Atrial Fibrillation/Flutter				
Y	2.03 (1.91-2.15)	<0.001	1.17 (1.12-1.23)	<0.001
N	Ref			
Postop Complications: Sepsis				
Y	5.04 (4.68-5.43)	<0.001	1.62 (1.51-1.75)	<0.001
N	Ref			

Table 4: Univariate and multivariate regression analysis for 30-day all-cause mortality.

	Univariate Analysis		**Multivariate Analysis**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Post-operative Hyponatremia				
Hyponatremic	4.96 (4.01-6.13)	<0.001	2.58 (2.01-3.30)	<0.001
Normatremic	Ref			
Service				
Ortho	2.43 (1.78-3.31)	<0.001	1.85 (1.28-2.66)	0.001
Other	Ref			
Age	1.02 (1.01 -1.02)	<0.001	0.99 (0.98-1.00)	0.004
Sex				
M	1.51 (1.22-1.86)	<0.001		
F	Ref			
BMI	0.96 (0.94-0.98)	<0.001	0.97 (0.95-1.00)	0.016
Race				
Asian	0.51 (0.30-0.86)	0.012	0.44 (0.25-0.78)	0.004
Black	1.44 (1.01-2.05)	0.044	1.13 (0.75-1.71)	0.551
Other	0.65 (0.32-1.33)	0.239	0.58 (0.27-1.25)	0.165
White	Ref			
ASA				
3	13.52 (5.02-36.39)	<0.001	10.03 (3.18-31.66)	<0.001
4,5	134.46 (49.75-363.41	<0.001	26.16 (8.11-84.41)	<0.001
1,2	Ref			
Elixhauser Score	1.13 (1.12-1.14)	<0.001	1.08 (1.06-1.10)	<0.001
Congestive Heart Disease				
Y	4.02 (2.87-5.63)	<0.001		
N	Ref			
Valvular Disease				
Y	2.60 (1.83-3.68)	<0.001		
N	Ref			
Pulmonary Circulatory Disorders				
Y	7.57 (5.37-10.67)	<0.001		
N	Ref			
Chronic Pulmonary Disease				
Y	1.14 (0.87-1.50)	0.325		
N	Ref			
Peripheral Vascular Disease				
Y	2.17 (1.46-3.23)	<0.001		

N	Ref			
Hypertension				
Y	1.11 (0.90-1.37)	0.325		
N	Ref			
Hypertension Complications				
Y	2.68 (2.04-3.52)	<0.001	0.52 (0.36-0.75)	<0.001
N	Ref			
Diabetes Mellitus				
Y	0.86 (0.59-1.25)	0.426		0.039
N	Ref			
Diabetes Mellitus Complications				
Y	2.66 (1.88-3.77)	<0.001	1.56 (1.02-2.37)	0.039
N	Ref			
Renal Failure				
Y	2.71 (2.03-3.63)	<0.001		
N	Ref			
Liver Disease				
Y	1.60 (1.08-2.39)	0.02	0.47 (0.29-0.77)	0.003
N	Ref			
Atrial Fibrillation/Flutter				
Y	2.69 (2.00-3.62)	<0.001		
N	Ref			
ESRD				
Y	6.66 (3.55-12.48)	<0.001		
N	Ref			
Coronary Stent				
Y	1.16 (0.71-1.90)	0.546		
N	Ref			
Anesthesia Hours	0.79 (0.74-0.84)	<0.001	0.80 (0.75-0.85)	<0.001
Surgery Hours	0.70 (0.65-0.75)	<0.001		
Estimated Blood Loss	1.004 (0.98-1.02)	0.708		
ICU Stay				
Y	16.27 (12.95-20.42)	<0.001	2.02 (1.42-2.87)	<0.001
N	Ref			
In-Hospital Thiazide Drugs				
Y	1.26 (0.79-2.01)	0.328		
N	Ref			
In-Hospital Potassium Sparing Drugs				
Y	1.73 (0.85-3.52)	0.13		
N	Ref			
In-Hospital NSAID				
Y	0.28 (0.22-0.36)	<0.001	0.43 (0.33-0.56)	<0.001
N	Ref			
In-Hospital Beta Blocker				
Y	2.00 (1.62-2.47)	<0.001		
N	Ref			
Postop Complications: Pulmonary				
Y	9.94 (8.04-12.29)	<0.001	3.31 (2.47-4.43)	<0.001

N	Ref			
Postop Complications: Stroke				
Y	15.55 (7.76-31.14)	<0.001		
N	Ref			
Postop Complications: Cardiac				
Y	9.57 (6.62-13.85)	<0.001	2.04 (1.26-3.29)	0.004
N	Ref			
Postop Complications: Thrombosis				
Y	5.97 (4.07-8.75)	<0.001		
N	Ref			
Postop Complications: Pulmonary Embolism				
Y	7.10 (4.13-12.21)	<0.001		
N	Ref			
Postop Complications: Atrial Fibrillation/Flutter				
Y	5.19 (3.64-7.41)	<0.001		
N	Ref			
Postop Complications: Sepsis				
Y	22.15 (16.48-29.78)	<0.001	1.93 (1.26-2.95)	0.002
N	Ref			

were also associated with higher risk of postoperative hyponatremia (Table 1). Lower BMIs were significantly associated with developing hyponatremia (25.5 *vs.* 27.2 kg/m^2; p<0.001). Several post-operative complications were found to be significantly associated with hyponatremia (Table 2).

Outcomes Analysis

Length of stay

The median length of stay for normonatremic patients was 4 days *vs.* 7 in the hyponatremia group (p<0.001). Multivariable analysis controlling for other factors independently associated with LOS found that patients that were hyponatremic had a 32% longer LOS compared to the non-hyponatremic group (exp(estimate) =1.32; 95% CI 1.30-1.35; p<0.001). There was a 20% increase in LOS for orthopedic patients compared to all other services (exp(estimate) =1.20; 95% CI 1.16-1.23; p<0.001) (Table 3). Similarly, within the orthopedic cohort, multivariable analysis controlling for other factors independently associated with LOS found that patients that were hyponatremic had a 27% longer LOS compared to the non-hyponatremic group (exp(estimate) =1.27; 95% CI=1.13-1.43; p<0.001) (Table 3).

Mortality

Compared to the non-hyponatremic group, the odds of 30-day mortality were significantly higher in the postoperative hyponatremic group (4.7% *vs.* 1.0%; univariable model OR=4.96; 95% CI 4.01-6.13; p<0.001). In multivariable analysis, postoperative hyponatremia patients were 2.58 times more likely to die within 30 days compared to those who did not have postoperative hyponatremia (OR=2.58; 95% CI 2.01-3.30; p<0.001). Within the orthopedic cohort, odds of 30-day mortality were significantly higher (OR=2.43; 95% CI 1.78-3.31; p<0.001) compared to the non-hyponatremic group. Risk of thirty-day mortality was also higher among the orthopedic surgery population compared to other services (OR=1.85; 95% CI 1.28-2.66; p=0.001) (Table 4). Mortality comparing non-hyponatremic groups to hyponatremic groups within the orthopedic population was not conducted due to only 9 events occurring.

Orthopedic cohort sub-analysis

Four patients were excluded because they underwent both hip and knee procedures. 419 patients were included in the sub-analysis comparing hip surgeries to knee surgeries. Median age of patients was 63.0 (IQR 51.0-70.0). Two-hundred thirty-one patients (55.13%) were female. Lower BMI was significantly associated with hyponatremia (25.3 *vs.* 26.8; p=0.012). Similarly, higher comorbidities were also associated with hyponatremia (21.0 *vs.* 16.0; p<0.001). Finally, hyponatremic patients generally had a higher ASA score (p=0.005).

Sub-analysis of hip *vs.* knee procedures within the orthopedic cohort found a significantly higher prevalence of hyponatremia post-operatively in hip procedure patients than knee procedures (21.47% *vs.* 11.39%; p=0.042) (Table 5). Length of stay (10 *vs.* 7 days; p<0.001), in-hospital beta blocker use (42.7% *vs.* 23.2%; p<0.001), and postoperative pulmonary embolism complication (4.9% *vs.* 1.2%; p=0.028) was significantly higher between the hyponatremic and normatremic group in this cohort (Table 6). There was no significant difference in LOS between knee and hip surgery patients while controlling for other factors associated with LOS, including post-op hyponatremia (Table 7).

Discussion

Our study of patients at a large cancer center found that postoperative hyponatremia is associated with 2.6 times greater risk of 30-day mortality and a 32% longer hospital stay. The increased mortality risk is consistent with recent studies suggesting that hyponatremia serves as an indicator of poor prognosis in several different cancer populations [22,23]. These findings underscore that not only does hyponatremia increase the risk of death; it dramatically increases hospital resource consumption. These findings suggest that prevention and prompt treatment of hyponatremia may help reduce hospital LOS. Future prospective studies must be conducted to explore this hypothesis.

Table 5: Prevalence, characteristics, and risk factors for postoperative hyponatremia within the orthopedic subgroup.

	Normatremic (N=337)	Hyponatremic (N=82)	Total (N=419)	P Value
Orthopedic Subgroup				
Hip	267 (79.23%)	73 (89.02%)	340 (81.15%)	0.042
Knee	70 (20.77%)	9 (10.98%)	79 (18.85%)	
Age				
Median (IQR)	62.0 (51.0-70.0)	64.0 (54.0-73.0)	63.0 (51.0-70.0)	0.096
Range	20.00-91.00	24.00-87.00	20.00-91.00	
Sex				
F	187 (55.49%)	044 (53.66%)	231 (55.13%)	0.765
M	150 (44.51%)	038 (46.34%)	188 (44.87%)	
BMI				
Median (IQR)	26.8 (23.6-31.6)	25.3 (22.5-29.9)	26.5 (23.3-31.2)	0.012
Range	14.20-53.80	13.70-48.90	13.70-53.80	
Race				
Asian	17 (5.35%)	7 (8.64%)	24 (6.02%)	0.229
black	30 (09.43%)	3 (3.70%)	33 (8.27%)	
other	7 (02.20%)	3 (03.70%)	10 (2.51%)	
white	264 (83.02%)	68 (83.95%)	332 (83.21%)	
Missing	19 (05.64%)	1 (01.22%)	20 (04.77%)	
ASA Physical Status				
P1	0 (0.00%)	1 (1.22%)	1 (0.24%)	
P2	43 (12.76%)	5 (6.10%)	48 (11.46%)	
P3	272 (80.71%)	62 (75.61%)	334 (79.71%)	
P4	22 (06.53%)	14 (17.07%)	36 (08.59%)	
ASA				
1,2	43 (12.76%)	6 (07.32%)	49 (11.69%)	0.005
3	272 (80.71%)	62 (75.61%)	334 (79.71%)	
4,5	22 (06.53%)	14 (17.07%)	36 (08.59%)	
Number of Discharge Diagnoses				
Median (IQR)	16.0 (11.0-22.0)	21.0 (15.0-27.0)	17.0 (11.0-23.0)	<0.001
Range	3.00-57.00	3.00-51.00	3.00-57.00	
Elixhauser Score				
Median (IQR)	12.0 (4.0-14.0)	12.0 (9.0-18.0)	12.0 (5.0-15.0)	<0.001
Range	0.00-36.00	0.00-34.00	0.00-36.00	
Congestive Heart Disease				
N	329 (97.63%)	076 (92.68%)	405 (96.66%)	0.025
Y	8 (2.37%)	6 (7.32%)	14 (3.34%)	
Valvular Disease				
N	322 (95.55%)	73 (89.02%)	395 (94.27%)	0.023
Y	15 (4.45%)	9 (10.98%)	24 (05.73%)	
Pulmonary Circulation Disorders				
N	330 (97.92%)	79 (96.34%)	409 (97.61%)	0.4
Y	7 (02.08%)	3 (03.66%)	10 (02.39%)	
Chronic Pulmonary Disease				
N	292 (86.65%)	71 (86.59%)	363 (86.63%)	0.988
Y	45 (13.35%)	11 (13.41%)	56 (13.37%)	

Peripheral Vascular Disease				
N	326 (96.74%)	79 (96.34%)	405 (96.66%)	0.859
Y	11 (03.26%)	3 (03.66%)	14 (3.34%)	
Hypertension				
N	214 (63.50%)	52 (63.41%)	266 (63.48%)	0.988
Y	123 (36.50%)	30 (36.59%)	153 (36.52%)	
Hypertension Complications				
N	310 (91.99%)	71 (86.59%)	381 (90.93%)	0.127
Y	27 (08.01%)	11 (13.41%)	38 (09.07%)	
Diabetes Mellitus				
N	311 (92.28%)	79 (96.34%)	390 (93.08%)	0.194
Y	26 (7.72%)	3 (03.66%)	29 (6.92%)	
Diabetes Mellitus Complications				
N	325 (96.44%)	80 (97.56%)	405 (96.66%)	0.612
Y	12 (3.56%)	2 (02.44%)	14 (3.34%)	
Renal Failure				
N	313 (92.88%)	77 (93.90%)	390 (93.08%)	0.743
Y	24 (7.12%)	5 (06.10%)	29 (06.92%)	
Liver Disease				
N	327 (97.03%)	81 (98.78%)	408 (97.37%)	0.375
Y	10 (2.97%)	1 (01.22%)	11 (02.63%)	
Atrial Fibrillation/Flutter				
N	306 (90.80%)	75 (91.46%)	381 (90.93%)	0.851
Y	31 (9.20%)	7 (8.54%)	38 (9.07%)	
ESRD				
N	334 (99.11%)	81 (98.78%)	415 (99.05%)	0.583
Y	3 (0.89%)	1 (1.22%)	4 (0.95%)	
Coronary Stent				
N	328 (97.33%)	77 (93.90%)	405 (96.66%)	0.121
Y	9 (02.67%)	5 (6.10%)	14 (3.34%)	

Hyponatremia in cancer patients depends on the cancer type and clinical setting [4]. The most frequent cause of hyponatremia in cancer patients is SIADH due to paraneoplastic secretion of antidiuretic hormone, chemotherapy induced renal toxicity, or as a complication of pituitary surgery [6]. SIADH is most commonly associated with small-cell lung cancer occurring in as many as 11% to 15% of patients, but is also associated with head and neck cancers, brain cancers, hematologic cancers, and many more [24-28]. Fuca et al. reported higher rates of in small cell lung cancer, prostate cancer, and biliary tract cancer [22]. Hansen et al. studies suggest that the degree of hyponatremia is associated with tumor burden [24,29].

The subset of patients who had orthopedic procedures experienced a hyponatremia rate of 15% *vs.* 13.5% in patients on other services. These findings indicate that prevalence of post-operative hyponatremia is generally lower than previously reported rates when examining cancer and orthopedic patients independently. Furthermore, within the oncologic patient population, orthopedics does not significantly increase rates of postoperative hyponatremia when compared to all other surgeries; denoting that salt levels should be monitored regardless of procedure completed for oncology patients. Chung et al. reported that only 4.4% of patients develop hyponatremia post-operatively, and the incidence within orthopedic patients to be lower at 3%. In this study we expected to find a higher prevalence in our cancer patient cohort. The lower prevalence in the Chung study can be explained by the generally less acceptable definition of hyponatremia that used a serum sodium cutoff of 130 mEQ/L [9,14,15,30]. Surgery induces electrolyte imbalances and other alterations of physiologic homeostasis. Arginine Vasopressin (AVP), the hormone implicated in SIADH, has been found to be released non-osmotically due to positive pressure ventilation, stress, nausea, pain, hypoglycemia, fever, decreases in intravascular volume, and cytokine release [31,32]. Similar to cancer, rates of hyponatremia differ based on the surgical site and type of operation. For instance, spine surgery has been found to have a higher rate of hyponatremia; it is theorized that the disruption of the neurohormonal axis results in SIADH [33].

Patients who had hip surgery had a higher prevalence of postoperative hyponatremia than patients who had knee surgery, but length of stay was no different. Higher rates of hyponatremia in total hip arthroplasty may be due to the greater stress to muscle and soft-tissue during hip dissection relative to total knee arthroplasty [9].

Table 6: Surgical and hospital stay factors for postoperative hyponatremia in the orthopedic subgroup.

	Normonatremia (N=337)	Hyponatremia (N=82)	Total (N=419)	P Value
Anesthesia Minutes				
Median (IQR)	326.0 (267.0-427.0)	335.5 (270.0-432.0)	327.0 (267.0-429.0)	0.725
Range	158.00-1114.00	178.00-980.00	158.00-1114.00	
Surgery Minutes				
Median (IQR)	215.0 (167.0-312.0)	223.5 (167.0-285.0)	216.0 (167.0-308.0)	0.959
Range	19.00-972.00	83.00-827.00	19.00-972.00	
Estimated Blood Loss (mL)				
Median (IQR)	500.0 (300.0-950.0)	525.0 (350.0-1000.0)	500.0 (300.0-1000.0)	0.366
Range	0.00-6200.00	10.00-4000.00	0.00-6200.00	
30-Day Mortality				
N	332 (98.52%)	78 (95.12%)	410 (97.85%)	0.057
Y	5 (1.48%)	4 (4.88%)	9 (2.15%)	
Length of Stay				
Median (IQR)	7.0 (5.0-10.0)	10.0 (7.0-19.0)	7.0 (5.0-12.0)	<0.001
Range	1.00-107.00	3.00-64.00	1.00-107.00	
ICU Stay				
N	328 (097.33%)	77 (93.90%)	405 (96.66%)	0.121
Y	9 (2.67%)	5 (6.10%)	14 (3.34%)	
In-Hospital Thiazide Drugs				
N	320 (94.96%)	78 (95.12%)	398 (94.99%)	0.951
Y	17 (5.04%)	4 (4.88%)	21 (5.01%)	
In-Hospital Potassium Sparing Drugs				
N	336 (099.70%)	81 (98.78%)	417 (99.52%)	0.353
Y	1 (0.30%)	1 (1.22%)	2 (0.48%)	
In-Hospital NSAIDS Drugs				
N	180 (053.41%)	47 (057.32%)	227 (54.18%)	0.525
Y	157 (46.59%)	35 (42.68%)	192 (45.82%)	
In-Hospital Beta Blocker Drugs				
N	259 (76.85%)	47 (57.32%)	306 (73.03%)	<0.001
Y	78 (23.15%)	35 (42.68%)	113 (26.97%)	
Postop Complication: Pulmonary				
N	306 (90.80%)	73 (89.02%)	379 (90.45%)	0.623
Y	31 (9.20%)	9 (10.98%)	40 (9.55%)	
Postop Complication: Stroke				
N	336 (99.70%)	81 (98.78%)	417 (99.52%)	0.353
Y	1 (0.30%)	1 (1.22%)	2 (0.48%)	
Postop Complication: Cardiac				
N	329 (97.63%)	79 (96.34%)	408 (97.37%)	0.514
Y	8 (2.37%)	3 (3.66%)	11 (2.63%)	
Postop Complication: Thrombosis				
N	324 (96.14%)	77 (93.90%)	401 (95.70%)	0.37
Y	13 (3.86%)	5 (6.10%)	18 (4.30%)	
Postop Complication: Pulmonary Embolism				
N	333 (98.81%)	78 (95.12%)	411 (98.09%)	0.028
Y	4 (1.19%)	4 (4.88%)	8 (1.91%)	
Postop Complication: Atrial Fibrillation/Flutter				

N	331 (98.22%)	81 (98.78%)	412 (98.33%)	0.722
Y	6 (1.78%)	1 (1.22%)	7 (1.67%)	
Postop Complication: Sepsis				
N	336 (99.70%)	80 (97.56%)	416 099.28%)	0.099
Y	1 (0.30%)	2 (2.44%)	3 0.72%)	

Table 7: Univariable and multivariate analysis for LOS within ortho cohort.

	Univariate analysis		Multivariate analysis	
	exp Estimate (95% CI)	**p-value**	**exp Estimate (95% CI)**	**p-value**
Postoperative Hyponatremia				
Y	1.43 (1.24- 1.64)	<0.001	1.27 (1.13- 1.43)	<0.001
N	Ref			
Orthopedic Surgery				
Knee	0.85 (0.74- 0.98)	0.026	0.96 (0.85- 1.08)	0.512
Hip	Ref			
Age	1.01 (1.00- 1.01)			
Sex				
M	0.94 (0.84- 1.06)	0.308		
F	Ref			
BMI	1.00 (0.99- 1.01)	0.726		
Race				
Asian	1.04 (0.81- 1.33)	0.768		
Black	1.19 (0.96- 1.47)	0.11		
Other	1.15 (0.80- 1.67)	0.447		
White	Ref			
ASA				
3	1.41 (1.20- 1.67)	<0.001	1.18 (1.02- 1.36)	0.031
4,5	2.35 (1.85- 2.99)	<0.001	1.64 (1.32- 2.04)	<0.001
1,2	Ref			
Elixhauser Score	1.03 (1.02- 1.04)	<0.001	1.01 (1.01- 1.02)	<0.001
Congestive Heart Disease				
Y	1.48 (1.08- 2.02)	<0.001		
N	Ref			
Valvular Disease				
Y	1.23 (0.97- 1.57)	0.09		
N	Ref			
Pulmonary Circulation Disorder				
Y	1.78 (1.24- 2.57)	0.002		
N	Ref			
Chronic Pulmonary Disease				
Y	1.16 (0.98- 1.37)	0.082		
N	Ref			
Peripheral Vascular Disease				
Y	1.23 (0.90- 1.69)	0.191		
N	Ref			
Hypertension				
Y	1.05 (0.93- 1.18)	0.455		
N	Ref			
Hypertension Complications				

Y	1.41 (1.16- 1.71)	<0.001		
N	Ref			
Diabetes Mellitus				
Y	1.42 (1.14- 1.77)	0.002	1.39 (1.16- 1.67)	<0.001
N	Ref			
Diabetes Mellitus Complication				
Y	1.49 (1.09- 2.03)	0.013	1.41 (1.09- 1.81)	0.009
N	Ref			
Renal Failure				
Y	1.19 (0.96- 1.49)	0.119		
N	Ref			
Liver Disease				
Y	1.13 (0.79- 1.61)	0.492		
N	Ref			
Atrial Fibrillation/Flutter				
Y	1.16 (0.96- 1.42)	0.128		
N	Ref			
ESRD				
Y	1.68 (0.94- 3.01)	0.078		
N	Ref			
Coronary Stent				
Y	1.48 (1.08- 2.03)	0.014		
N	Ref			
Anesthesia Hours	1.06 (1.03- 1.08)	<0.001	1.03 (1.01- 1.06)	0.007
Surgery Hours	1.05 (1.03- 1.08)	<0.001		
Estimated Blood Loss (per 100 units)	1.02 (1.01- 1.02)	<0.001	1.01 (1.00- 1.01)	0.039
ICU Stay				
Y	3.12 (2.33- 4.20)	<0.001	1.51 (1.13- 2.01)	0.005
N	Ref			
In-Hospital Thiazide Drugs				
Y	1.05 (0.81- 1.36)	0.7		
N	Ref			
In-Hospital Potassium Sparing Drugs				
Y	1.66 (0.73- 3.77)	0.225		
N	Ref			
In-Hospital NSAID Drugs				
Y	0.94 (0.84- 1.06)	0.32		
N	Ref			
In-Hospital Beta Blocker Drugs				
Y	1.22 (1.08- 1.39)	0.002		
N	Ref			
Postoperative Complications: Pulmonary				
Y	1.85 (1.54- 2.23)	<0.001	1.33 (1.12- 1.58)	0.001
N	Ref			
Postoperative Complications: Stroke				
Y	2.36 (1.04- 5.35)	<0.001		
N	Ref			
Postoperative Complications: Cardiac				

Y	1.90 (1.34- 2.70)	<0.001		
N	Ref			
Postoperative Complications: Thrombosis				
Y	1.94 (1.48- 2.55)	<0.001	1.54 (1.22- 1.93)	<0.001
N	Ref			
Postoperative Complications: Pulmonary Embolism				
Y	1.80 (1.19- 2.70)	0.005		
N	Ref			
Postoperative Complications: Atrial Fibrillation/Flutter				
Y	1.82 (1.18- 2.82)	0.007		
N	Ref			
Postoperative Complications: Sepsis				
Y	1.96 (1.00- 3.82)	0.048		
N	Ref			

Postoperative hyponatremia is preventable and treatable [34]. Anesthesiologists should request preoperative electrolyte panels in patients at risk, such as elderly patients taking thiazide diuretics. Balanced crystalloid intravenous solutions should be used instead of dextrose-containing fluids that quickly become hypotonic once the dextrose is metabolized. Physicians in the PACU should have a high index of suspicion for hyponatremia when evaluating a postoperative encephalopathic patient. Indeed, symptoms of hyponatremia can be easily confused with a neurologic event such as postoperative stroke.

Study Limitations

Limitations of this study include its retrospective approach and reliance on administrative data for assessment of comorbidities. Our hospital does not measure preoperative electrolyte concentrations unless clinically indicated, in line with the American Society of Anesthesiologists practice advisory on preanesthesia testing, so our study was unable to exclude patients with preexisting hyponatremia [35]. Also, we were unable to include data on the likely cause of hyponatremia in these patients.

Hyponatremia was defined as <133 mEq/L at our institution, but usually is defined below 135 mEq/L or other values in different institutions, which may lead to fewer patients in our study population being diagnosed with hyponatremia. We controlled for hyperglycemia using glucose values, but sodium measurements can also be influenced by protein and lipid concentrations.

Conclusion

In conclusion, our study on postoperative hyponatremia in patients with cancer undergoing orthopedic surgery and other surgeries reveal an independent association between hyponatremia status and longer hospital stay and thirty-day mortality. This association also existed in cancer patients who underwent orthopedic surgery. There is a higher prevalence of postoperative hyponatremia in patients undergoing hip procedures relative to patients undergoing knee procedures. Further studies are warranted to explore the associations between hyponatremia risk factors and ultimately to determine the cause of hyponatremia in this patient population.

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