Major Risk Factors of Mortality in Adult and Elderly Patients Emergently Admitted for Intestinal Fistulas, Excluding the Rectum and Anus

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ABSTRACT

Introduction: In the United States, intestinal fistulas accounts for $500 million (USD) of healthcare expenditures and 28,000 admissions annually. They are also associated with significant morbidity and mortality. Despite the high prevalence of intestinal fistulas, risk factors of mortality have yet to be fully elucidated. The aim of this study was to identify risk factors of mortality in emergently admitted patients with fistulas of the intestine, excluding the rectum and anus.

Materials and Methods: Adult and elderly patients emergently admitted with intestinal fistulas, between 2004–2014 were investigated using the National Inpatient Sample Database, ICD-9-CM code 569.81. Clinical outcomes, therapeutic management, demographics, and comorbidities were collected. Associations between mortality and all other variables were established via univariable and multivariable logistic regression models. The final multivariable regression model elucidated the odds ratios (95% confidence interval, p-value) of pertinent mortality risk factors.

Results: A total of 7,377 patients were included, of which the average adult and elderly ages were 48.9 and 74.6 years, respectively. Of these patients, 4,241 (57.5%) were female and 3,136 (42.5%) were male. Elderly patients demonstrated a higher mortality rate than adult patients—4.5% and 1.7%, respectively. In the adult group, the odds ratio for mortality was 1.020 for hospital length of stay in days (95% CI: 1.015–1.026, p<0.001), 1.035 for age (95% CI: 1.011–1.060, p=0.004), and 1.033 for days to the first procedure (95% CI: 1.021–1.044, p<0.001), among others. For the elderly group, the odds ratio for mortality was 1.012 for hospital length of stay in days

(95% CI: 1.005–1.019, p=0.001), 1.075 for age (95% CI: 1.050–1.101, p<0.001), and 1.026 for days to the first procedure (95% CI: 1.009–1.043, p=0.002), among others.

Conclusion: In adult and elderly patients emergently admitted for intestinal fistulas, multiple comorbidities were risk factors for in-hospital mortality. In the elderly cohort, increased age and increased days to operation were additional risk factors for in-hospital mortality.

INTRODUCTION

Intestinal fistulas, excluding the rectum and anus, contributes to a high number of admissions, morbidity, and mortality worldwide.[1–12] There are a broad range of causes including surgical complications, diverticular disease, irritable bowel syndrome, malignancy, radiation, or injury due to trauma or foreign bodies.[13] Intestinal fistulas are considered a complication rather than a separate disease, and they are most commonly caused by surgical complications.[13] The incidence of postoperative intestinal fistulas ranges from 1.1–5.5% and varies according to surgery type.[1,14,15] This incidence increases drastically to 15–50% in special populations, such as patients with Crohn's disease or irritable bowel syndrome.[13,16,17] This increased incidence originates from an epithelial defect that occurs during chronic inflammation.[16] After undergoing epithelial to mesenchymal transition, intestinal epithelial cells in Crohn's disease patients penetrate into deeper tissue layers, causing further damage and connections to other organs or the body surface.[16]

The occurrence of intestinal fistulas after abdominal operation or trauma leads to prolonged hospital length of stay (HLOS), the potential need for reoperations, increased risk of other complications, a marked increase in healthcare costs, and potential death.[1,4,18] In the United States, intestinal fistulas accounted for 317,000 hospital admissions from 2004 to 2014, and costs totaled more than $500 million (USD) annually.[18] The mortality rate of intestinal fistulas ranges from 5–48% and varies considerably due to the heterogenous nature and accompanying comorbidities seen with this condition.[1–4,19] Instead of identifying a single prognostic factor that increases the risk of mortality in intestinal fistulas patients, this study categorized various risk factors of mortality due to the complex etiology and variable clinical manifestations of this condition.

The pathogenesis of intestinal fistulas is multifactorial, with the majority being post surgical. However, there can be a complication of an underlying disease (inflammatory disease, neoplasm), post-radiation treatment, or due to injury.[13] Treatment protocols consist of nutritional and metabolic support and removal of—or addressing—the etiologic factors. In general, treatment protocols are divided into the conservative/nonoperative approach and the operative approach.[13,20] Priorities in the management of intestinal fistulas include restoration of blood volume and correction of fluid, electrolytes, and acid-base imbalances; control of infection and sepsis with appropriate antibiotics and drainage of abscesses; initiation of GI tract rest including secretory inhibition and nasogastric suction; control and collection of fistula drainage with protection of the surrounding skin; and provision of optimal nutrition by total parenteral nutrition (TPN) or enteral nutrition (EN) (or both).[20] The timing of surgical treatment is controversial, but most surgeons tailor their surgical treatment based on etiology, fistulas output, the anatomy of fistulas (enterocutaneous fistulas [ECFs] or enteroatmospheric fistulas [EAFs]), if it is associated with a frozen and hostile abdomen, and finally on the physiologic status of the patients.[21] Overall, the senior author prefers to intervene early rather late, particularly in fistulas that will not close with conservative management, such as multiple EAF and those associated with frozen abdomen.[22] A well-established strategy on the management of intestinal fistulas is focused on the control of sepsis, optimization of nutritional status, wound care, establishing fistula anatomy, and the timing of surgery. Surgical strategy (SOWATS-protocol) has been described in the literature to help guide the treatment of these patients.[22,23]

A significant number of patients who develop postoperative fistulas have major complex abdominal wall defects and require complex abdominal wall defects reconstruction.[24,25] The three important missing aspects to the management of ECF by SOWATS approach include initial diagnosis, postoperative care, and long-term follow up. To this end, we have modified it to a nine-step strategy known as ISOWATS PL. The ISOWATS PL stands for I=identification of postoperative fistulas, S=sepsis control, and eradication, O=Optimization of nutrition, W=wound care, A=redefining the anatomy, T=timing of operation or takedown of ECF, S=surgical approach, P=postoperative care, and L=long-term follow up.[26] Further details on each of these steps is beyond the scope of the article, but they stress that treatment EC of EA fistulas may be very complex.

It is crucial to recognize the risk factors of mortality in intestinal fistulas patients and identify higher-risk patients. We suspect that increased patient age, hospital length of stay, and time to first procedure are significant risk factors for mortality, as all three have been associated with complications and mortality. Identifying the risk factors specific for intestinal fistulas patients will allow earlier and definitive treatment. The primary aim of this study was to identify potential predictors of mortality in emergently admitted patients with the primary diagnosis of fistulas of the intestine, excluding the rectum and anus.

MATERIALS AND METHODS

The study analyzed data from the National Inpatient Sample repository for patients who were emergently admitted with the primary diagnosis of fistulas of the intestine, excluding the rectum and anus (ICD-9-CM Diagnosis Code 569.81) from 2004 to 2014. The National Inpatient Sample is a government-funded database created by the Agency for Healthcare Research and Quality (AHRQ). AHRQ sponsored the Healthcare Cost and Utilization project to create nationally collected population-based data in standardized formats. This retrospective cohort study extracted data with the following inclusion criteria: (1) non-elderly adult patients (ages 18–64 years) and elderly patients (65+ years), (2) with the primary diagnosis of intestinal fistulas, excluding the rectum and anus, (3)

who underwent emergency admission from National Inpatient Sample 2004-2014.

The data collected in this study were analyzed and stratified according to parameters including age differences, sex, and clinical outcomes (survived vs. deceased). Patient attributes were further assessed based upon the following factors: race (White, Black, Hispanic, Asian/Pacific Islander, Native American, other), income quartile, insurance status (private insurance, Medicare, Medicaid, self-pay, no charge, other), hospital location (rural, urban non-teaching, urban teaching), and associated diagnoses, hospital length of stay, time to first surgical procedure, and total charges in USD (Table I).

Statistical analysis

The independent variables were stratified in two ways: (1) according to age, either adult or elderly and (2) survived patients vs. deceased ones within each age group. The dependent variable was mortality. Subsequent to stratification, the descriptive and analytical data were utilized to conduct more nuanced analyses demonstrated through tables. The results are presented alongside the average, standard deviation (SD), confidence interval set at 95% (CI), and p-values (less than 0.05 considered significant). The ability to predict mortality based upon individual variables was demonstrated using a univariable logistic regression analysis. Finally, evaluation of mortality and risk factors were further investigated through a multivariable backward logistic regression analysis, in which risk factors were removed via stepwise backward elimination. For these analyses, SPSS version 24 (SPSS Inc., Chicago, Illinois) and R software (Foundation for Statistical Computing, Vienna, Austria) were used.

RESULTS

Age, gender, race, and comorbidities differences

Between 2004 and 2014, 7,377 patients were emergently admitted with the primary diagnosis of intestinal fistulas, excluding the rectum and anus. Of these patients, 4,241 (57.5%) were females and 3,136 (42.5%) were males (Table I). There were 2,789 (37.8%) patients in the elderly group and 4,588 (62.2%) patients in the adult group. The elderly group consisted of 1,735 females (62.2%), and the adult group consisted of 2,506 females (54.6%). The average age (SD) of the adult who survived and died was 48.79 (11.37) and 52.59 (10.37), respectively (Table I). The average age (SD) of elderly patients who survived and died was 74.42 (7.00) and 78.46 (7.90), respectively. The majority of the adult patients were white, had private insurance, and were treated in a government or private hospital. Most of the elderly patients were white, had Medicare, and were treated in a government or private hospital. For adult and elderly patients, Quartile 1 for income was the most common for all patients, and Quartile 4 was the least common. The rates of comorbidities between the adult and the elderly group are depicted in Table I. In the surviving adult group, the most common comorbidities included hypertension, fluid and electrolyte disbalance, deficiency anemias, recent weight loss, uncomplicated diabetes, depression, chronic pulmonary disease, and obesity. In the surviving elderly group, the most common comorbidities were similar to the surviving adult group, with the addition of hypothyroidism. The parameters of interest including age differences, race, income quartile, insurance, hospital location, other diagnoses, hospital length of stay, time to first surgical procedure, and total charges in US dollars are displayed in Table I.

Mortality

Adult patients

A stratified analysis based on outcome categories (survived vs. deceased) is shown in Table I. In the adult group, 76 (1.7%) patients died as a result of their intestinal fistulas. Deceased patients in the adult group were 3.8 years older than the surviving patients. Of the deceased patients, 48 were female (63.2%) and 28 were male (36.8%), with a similar mean age. When comparing the deceased to the surviving, significant differences were identified in terms of comorbidities. Adult patients who died exhibited significantly higher rates of comorbidities including coagulopathy, valvular disease, renal failure, fluid and electrolyte disorders, metastatic cancer, rheumatoid arthritis, and congestive heart failure when compared to surviving adult patients. Adult patients that died had a longer average hospital length of stay when compared to adult patients that survived—42.68 days compared to 13.39 days. Additionally, there was a significant difference between the surviving and the deceased cohort of the length of time to the first operation. In the adult group, the deceased patients had an average of 19.84 days since the first procedure, compared to 4.65 days in the surviving patients. The surviving adults had a higher percentage of individuals on private insurance, Medicaid, and self-pay when compared to deceased adults. Finally, there was a statistically significant difference in the total amount of hospital charges (US dollars) between the surviving and the deceased. In the adult group, there was an average of $274,496 more spent on healthcare costs in the deceased group.

Elderly patients

A stratified analysis based on outcome categories (survived vs. deceased) is shown in Table I. In the elderly group, 125 (4.5%) patients died as a result of their intestinal fistulas. Deceased patients in the elderly group were four years older than the surviving patients. Of the deceased patients, 91 were female (72.8%) and 34 were male (27.2%). When comparing the deceased to the surviving, significant differences were found in the comorbidities. Elderly patients who died displayed significantly higher rates of coagulopathy, renal failure, fluid and electrolyte disorders, congestive heart failure, and hypertension when compared to the surviving adult patients. In the elderly patient cohort, patients who died also had a longer hospital length of stay (HLOS) when compared to the elderly patients who survived—18.80 days versus 13.21 days. There was also a significant difference between the surviving and the dead cohort of the length of time to the first procedure. In the elderly group, the dead patients had an average of 7.00 days since the first procedure, compared to 4.40 days in the surviving patients. In terms of insurance status, there were no significant differences noted in the elderly population. In terms of healthcare costs, there was an average of $107,161 more spent on healthcare costs than in the deceased group.

Risk factors of mortality

The variables in Table I were assessed with a univariable logistic regression for further characterization of differences between survived and deceased male and female patients with fistulas of the intestine, excluding the rectum and anus. Table II depicts the univariable logistic regression analysis for emergently admitted adult (18–64 years) patients with

Table I
Characteristics of emergency admitted adult (18–64) and elderly (65+ years) patients with the diagnosis of intestinal fistulas, excluding rectum and anus (NIS 2004–2014)

		Adult, N (%) N=4,588			Elderly, N (%) N=2,789		
		Survived, N (%)	Died, N (%)	p-value	Survived, N (%)	Died, N (%)	p-value
All Cases		4,512 (98.3%)	76 (1.7%)		2,664 (95.5%)	125 (4.5%)	
Sex, Female		2,458 (54.5%)	48 (63.2%)	0.1	1,644 (61.7%)	91 (72.8%)	**0.012**
Race	**White**	2,701 (70.6%)	46 (71.9%)	0.7	1,856 (80.6%)	86 (80.4%)	0.4
	Black	550 (14.4%)	11 (17.2%)		186 (8.1%)	5 (4.7%)	
	Hispanic	391 (10.2%)	5 (7.8%)		170 (7.4%)	12 (11.2%)	
	Asian/Pacific Islander	52 (1.4%)	0 (0%)		31 (1.3%)	1 (0.9%)	
	Native American	25 (0.7%)	1 (1.6%)		8 (0.3%)	1 (0.9%)	
	Other	107 (2.8%)	1 (1.6%)		51 (2.2%)	2 (1.9%)	
Income	**Quartile 1**	1,313 (29.8%)	24 (33.3%)	0.8	721 (27.5%)	36 (29.3%)	0.2
Quartile	**Quartile 2**	1,181 (26.8%)	20 (27.8%)		676 (25.8%)	40 (32.5%)	
	Quartile 3	1,001 (22.7%)	16 (22.2%)		625 (23.8%)	27 (22.0%)	
	Quartile 4	911 (20.7%)	12 (16.7%)		601 (22.9%)	20 (16.3%)	
	Private Insurance	1,919 (42.6%)	27 (35.5%)	**0.010**	204 (7.7%)	13 (10.4%)	0.1
Insurance	**Medicare**	988 (21.9%)	27 (35.5%)		2,388 (89.9%)	106 (84.8%)	
	Medicaid	1,038 (23.0%)	17 (22.4%)		30 (1.1%)	2 (1.6%)	
	Self-Pay	306 (6.8%)	0 (0%)		9 (0.3%)	1 (0.8%)	
	Other	33 (0.7%)	1 (1.3%)		25 (0.9%)	3 (2.4%)	
	Government or Private	2,178 (48.3%)	40 (52.6%)	0.5	1,212 (45.5%)	59 (47.2%)	0.2
Hospital	**Government: Non-federal**	419 (9.3%)	8 (10.5%)		206 (7.7%)	5 (4.0%)	
Ownership	**Private: Not-for-Profit**	1,511 (33.5%)	26 (34.2%)		957 (35.9%)	42 (33.6%)	
	Private: Investor	347 (7.7%)	2 (2.6%)		248 (9.3%)	15 (12.0%)	
	Private: NFP or Investor	57 (1.3%)	0 (0%)		41 (1.5%)	4 (3.2%)	
Hospital Bed	**Small**	447 (9.9%)	5 (6.6%)	0.6	329 (12.3%)	14 (11.2%)	0.8
Size	**Medium**	963 (21.3%)	15 (19.7%)		586 (22.0%)	30 (24.0%)	
	Large	3,102 (68.8%)	56 (73.7%)		1,749 (65.7%)	81 (64.8%)	
Comorbidities	**AIDS**	11 (0.2%)	1 (1.3%)	0.2	0 (0%)	0 (0%)	
	Alcohol Abuse	114 (2.5%)	1 (1.3%)	0.9	27 (1.0%)	0 (0%)	0.6
	Deficiency Anemias	1,170 (25.9%)	18 (23.7%)	0.7	839 (31.5%)	39 (31.2%)	0.9
	Rheumatoid Arthritis	122 (2.7%)	5 (6.6%)	**0.041**	86 (3.2%)	7 (5.6%)	0.2
	Chronic Blood Loss	58 (1.3%)	1 (1.3%)	0.9	57 (2.1%)	4 (3.2%)	0.4
	Congestive Heart Failure	151 (3.3%)	6 (7.9%)	**0.031**	327 (12.3%)	28 (22.4%)	**0.001**
	Chronic Pulmonary Disease	675 (15.0%)	11 (14.5%)	0.9	577 (21.7%)	22 (17.6%)	0.3
	Coagulopathy	145 (3.2%)	17 (22.4%)	**<0.001**	90 (3.4%)	21 (16.8%)	**<0.001**
	Depression	685 (15.2%)	8 (10.5%)	0.3	304 (11.4%)	10 (8.0%)	0.2
	Diabetes, Uncomplicated	766 (17.0%)	12 (15.8%)	0.8	640 (24.0%)	22 (17.6%)	0.1
	Diabetes, Chronic Complications	87 (1.9%)	0 (0%)	0.4	98 (3.7%)	3 (2.4%)	0.6
	Drug Abuse	192 (4.3%)	2 (2.6%)	0.8	15 (0.6%)	0 (0%)	0.9
	Hypertension	1,573 (34.9%)	26 (34.2%)	0.9	1,633 (61.3%)	63 (50.4%)	**0.015**
	Hypothyroidism	357 (7.9%)	4 (5.3%)	0.5	428 (16.1%)	23 (18.4%)	0.5
	Liver Disease	151 (3.3%)	5 (6.6%)	0.1	44 (1.7%)	4 (3.2%)	0.2
	Lymphoma	22 (0.5%)	2 (2.6%)	0.1	26 (1.0%)	3 (2.4%)	0.1
	Fluid/Electrolyte Disorders	1,362 (30.2%)	47 (61.8%)	**<0.001**	937 (35.2%)	68 (54.4%)	**<0.001**
	Metastatic Cancer	389 (8.6%)	12 (15.8%)	**0.028**	288 (10.8%)	15 (12.0%)	0.7
	Other Neurological Disorders	192 (4.3%)	5 (6.6%)	0.3	156 (5.9%)	11 (8.8%)	0.2
	Obesity	632 (14.0%)	5 (6.6%)	0.1	271 (10.2%)	8 (6.4%)	0.2
	Paralysis	84 (1.9%)	1 (1.3%)	0.9	40 (1.5%)	4 (3.2%)	0.1
	Peripheral Vascular Disorders	93 (2.1%)	0 (0%)	0.4	173 (6.5%)	7 (5.6%)	0.7
	Psychoses	269 (6.0%)	7 (9.2%)	0.2	74 (2.8%)	2 (1.6%)	0.6
	Pulmonary Circulation Disorders	46 (1.0%)	1 (1.3%)	0.6	71 (2.7%)	6 (4.8%)	0.2
	Renal Failure	287 (6.4%)	19 (25.0%)	**<0.001**	315 (11.8%)	31 (24.8%)	**<0.001**
	Solid Tumor	220 (4.9%)	4 (5.3%)	0.8	208 (7.8%)	10 (8.0%)	0.9
	Peptic Ulcer	6 (0.1%)	0 (0%)	0.9	0 (0%)	1 (0.8%)	**0.045**
	Valvular Disease	58 (1.3%)	5 (6.6%)	**<0.001**	101 (3.8%)	5 (4.0%)	0.9
	Weight Loss	1,143 (25.3%)	41 (53.9%)	**<0.001**	780 (29.3%)	45 (36.0%)	0.1
		Mean (SD)	**Mean (SD)**	**p-value**	**Mean (SD)**	**Mean (SD)**	**p-value**
	Age, Years	48.79 (11.37)	52.59 (10.37)	**0.004**	74.43 (7.00)	78.46 (7.90)	**<0.001**
	Time to First Procedure, Days	4.65 (9.43)	19.84 (47.60)	**0.014**	4.40 (7.53)	7.00 (12.38)	**0.039**
	Hospital length of Stay, Days	13.39 (18.68)	42.68 (57.05)	**<0.001**	13.21 (16.27)	18.80 (18.32)	**0.001**
	Total Charges, Dollars	82,816 (131,214)	357,312 (359,405)	**<0.001**	80,302 (117,518)	187,463 (247,792)	**<0.001**

intestinal fistulas, which illustrates the associations between mortality and different risk factors. Table III depicts the univariable logistic regression analysis for emergently admitted elderly (65+ years) patients with intestinal fistulas, and it outlines the associations between mortality and various risk factors. Of the patients in the adult group, the following factors were measured in the multivariable logistic regression models: comorbidities such as coagulopathy, fluid and electrolyte disorders, renal failure, AIDS, metastatic cancer, and valvular disease. Of the patients in the elderly group, the following factors were measured in the multivariable logistic regression models: age, sex, days to first procedure, and comorbidities such as coagulopathy, fluid and electrolyte disorders, renal failure, congestive heart failure, and paralysis. The results of a multivariable logistic regression analysis with backward elimination for both adults and elderly patients are shown in Table IV. Age and days to first procedure were used as continuous variables in this study, which allowed for a better understanding of the relationship between these variables and mortality in fistulas patients.

Adult patients

In the adult cohort, comorbidities such as coagulopathy, fluid/electrolyte disorders, metastatic cancer, renal failure, and valvular disease displayed statistically significant associations with mortality (Tables II and IV). Adult patients with coagulopathy had a five-fold increase in the odds of mortality, while fluid/electrolyte disorders increased the odds of mortality by 2.2-fold. Patients with renal failure had a 2.9-fold increase in the odds of mortality, while patients with metastatic cancer increased the odds of mortality by three-fold, and valvular disease increased the odds of mortality by 3.5-fold.

Elderly patients

In the elderly group, age, days to the first procedure, and comorbidities such as coagulopathy, fluid/electrolyte disorders, renal failure, and paralysis presented statistically significant associations with mortality (Tables III and IV). Each additional day of HLOS from the first procedure increased the odds of mortality by 3%. For every additional year of age, patients demonstrated an increased odds of mortality by 7.0%. Patients with coagulopathy had a 4.8-fold increase in the odds of mortality, while fluid and electrolyte disorders increased the mortality odds by 2.1-fold. The presence of renal failure increased the odds of mortality by 2.2-fold, and pre-existing paralysis increased the mortality odds by four-fold.

Table II
Univariable logistic regression analysis to evaluate the associations between mortality and different factors in emergency admitted adult nonelderly (18–64 years) patients with the diagnosis of intestinal fistulas excluding rectum and anus (NIS 2004–2014)—mortality was the dependent variable*

		Univariable Logistic Regression	
		OR (95% CI)	p-value
Hospital Length of Stay, Days		1.020 (1.015, 1.026)	**<0.001**
Age, Years		1.035 (1.011, 1.060)	**0.004**
Sex, Female		1.429 (0.893, 2.286)	0.1
Days to the First Procedure		1.033 (1.021, 1.044)	**<0.001**
Comorbidities	**AIDS**	5.456 (0.696, 42.797)	0.1
	Coagulopathy	8.678 (4.936, 15.258)	**<0.001**
	Fluid/Electrolyte Disorders	3.748 (2.349, 5.980)	**<0.001**
	Metastatic Cancer	1.987 (1.063, 3.714)	**0.031**
	Renal Failure	4.907 (2.880, 8.360)	**<0.001**
	Valvular Disease	5.408 (2.106, 13.888)	**<0.001**
	Rheumatoid Arthritis	2.534 (1.005, 6.388)	**0.049**
	Chronic Blood Loss	1.024 (0.140, 7.490)	0.9
	Congestive Heart Failure	2.475 (1.059, 5.788)	**0.036**
	Drug Abuse	0.608 (0.148, 2.496)	0.5
	Liver Disease	2.034 (0.810, 5.110)	0.1
	Lymphoma	5.516 (1.274, 23.886)	**0.022**
	Other Neurological Disorders	1.585 (0.633, 3.969)	0.3
	Psychoses	1.600 (0.728, 3.516)	0.2
	Weight Loss	3.453 (2.188, 5.448)	**<0.001**
Race	**White [Ref]**		0.9
	Black	1.174 (0.604, 2.282)	0.6
	Hispanic	0.751 (0.297, 1.901)	0.6
	Asian/Pacific Islander	0 (0)	0.9
	Native American	2.349 (0.312, 17.704)	0.4
	Other	0.549 (0.075, 4.017)	0.6
Income Quartile	**Quartile 4 [Ref]**		0.8
	Quartile 1	1.388 (0.690, 2.789)	0.4
	Quartile 2	1.286 (0.625, 2.644)	0.5
	Quartile 3	1.213 (0.571, 2.579)	0.6
Insurance	**Private Insurance [Ref]**		0.3
	Medicare	1.942 (1.133, 3.329)	**0.016**
	Medicaid	1.164 (0.632, 2.146)	0.6
	Self-Pay	0 (0)	0.9
	No Charge	2.154 (0.284, 16.323)	0.5
	Other	1.275 (0.442, 3.677)	0.7
Hospital Ownership	**Government or Private [Ref]**		0.6
	Government: Non-federal	1.040 (0.483, 2.237)	0.9
	Private: Not-for-Profit	0.937 (0.569, 1.542)	0.8
	Private: Investor	0.314 (0.076, 1.304)	0.1
	Private: NFP or Investor	0 (0)	0.9
Hospital Bed Size	**Small [Ref]**		0.6
	Medium	1.393 (0.503, 3.855)	0.5
	Large	1.614 (0.643, 4.051)	0.3

Bold indicates result is statistically significant

DISCUSSION

The primary aim of this study was to assess associations between patient demographics, socioeconomic status, postoperative hospital length of stay, patient age, days to the first procedure, comorbidities,

Table III
Univariable logistic regression analysis to evaluate the associations between mortality and different factors in emergency admitted elderly (65+ years) patients with the diagnosis of intestinal fistulas, excluding rectum and anus (NIS 2004-2014)—mortality was the dependent variable

		Univariable Logistic Regression	
		OR (95% CI)	p-value
Hospital Length of Stay, Days		1.012 (1.005, 1.019)	**0.001**
Age, Years		1.075 (1.050, 1.101)	**<0.001**
Sex, Female		1.661 (1.111, 2.481)	**0.013**
Days to the First Procedure		1.026 (1.009, 1.043)	**0.002**
Comorbidities	Congestive Heart Failure	2.063 (1.334, 3.191)	**0.001**
	Coagulopathy	5.775 (3.455, 9.654)	**<0.001**
	Fluid/Electrolyte Disorders	2.199 (1.533, 3.154)	**<0.001**
	Paralysis	2.169 (0.764, 6.159)	0.2
	Renal Failure	2.459 (1.612, 3.753)	**<0.001**
	Rheumatoid Arthritis	1.778 (0.805, 3.927)	0.2
	Chronic Blood Loss	1.512 (0.540, 4.235)	0.4
	Hypothyroidism	1.178 (0.741, 1.874)	0.5
	Liver Disease	1.968 (0.696, 5.567)	0.2
	Lymphoma	2.495 (0.745, 8.357)	0.1
	Metastatic Cancer	1.125 (0.647, 1.956)	0.7
	Other Neurological Disorders	1.551 (0.818, 2.941)	0.2
	Obesity	0.604 (0.292, 1.249)	0.2
	Peripheral Vascular Disorders	0.854 (0.392, 1.859)	0.7
	Pulmonary Circulation Disorders	1.841 (0.784, 4.322)	0.2
	Solid Tumor	1.027 (0.530, 1.990)	0.9
	Valvular Disease	1.057 (0.423, 2.644)	0.9
	Weight Loss	1.359 (0.934, 1.976)	0.1
Race	White [Ref]		0.5
	Black	0.580 (0.233, 1.447)	0.2
	Hispanic	1.523 (0.816, 2.843)	0.2
	Asian/Pacific Islander	0.696 (0.094, 5.160)	0.7
	Native American	2.698 (0.334, 21.812)	0.4
	Other	0.846 (0.203, 3.534)	0.8
Income Quartile	Quartile 4 [Ref]		0.2
	Quartile 1	1.500 (0.859, 2.619)	0.2
	Quartile 2	1.778 (1.028, 3.075)	**0.040**
	Quartile 3	1.298 (0.720, 2.339)	0.4
Insurance	Private Insurance [Ref]		0.3
	Medicare	0.697 (0.385, 1.261)	0.2
	Medicaid	1.046 (0.225, 4.866)	0.9
	Self-Pay	1.744 (0.205, 14.830)	0.6
	Other	1.883 (0.502, 7.065)	0.4
Hospital Ownership	Government or Private [Ref]		0.3
	Government: Non-federal	0.499 (0.198, 1.257)	0.1
	Private: Not-for-Profit	0.902 (0.602, 1.351)	0.6
	Private: Investor	1.242 (0.694, 2.226)	0.5
	Private: NFP or Investor	2.004 (0.695, 5.781)	0.2
Hospital Bed Size	Small [Ref]		0.8
	Medium	1.203 (0.629, 2.301)	0.6
	Large	1.088 (0.610, 1.943)	0.8

Bold indicates result is statistically significant

and mortality in emergently admitted adult and elderly patients with the primary diagnosis of intestinal fistulas, excluding the rectum and anus. The reported mortality rate of emergently admitted intestinal fistulas patients varies, but ranges from 5–48%.[1–4] It is difficult to conclude the presence of a single prognostic factor that increases the risk of mortality in patients with the primary diagnosis of an intestinal fistulas due to the heterogenous nature and variable clinical manifestations of this condition.[19] Our data has demonstrated that in the emergency admission of patients with the diagnosis of fistulas of the intestine, excluding the rectum and anus, hospital length of stay, days to the first procedure, and patient age were the leading risk factors for mortality.

The impact of hospital length of stay on mortality risk

While hospital length of stay was a significant predictor of mortality in the univariable regression analysis for the adult and elderly cohorts, this variable was not used in the final multivariable regression model due to collinearity. Hospital length of stay was over-correlated with "Days to the First Procedure," which would decrease the accuracy of the final multivariable model if both used in the model. Because of this, the hospital length of stay variable was selectively removed from the final regression model.

Longer hospital length of stay was associated with adverse outcomes in intestinal fistulas patients. Better functional outcomes and lower mortality are associated with shorter hospital length of stay, which suggests an advantage of decreasing hospital length of stay, and early operation.[21,27–40] This association has been proven multiple times in similar studies from our group who also utilized data from the National Inpatient Sample.[28,34,36] In a study that identified mortality risk factors in patients emergently admitted with paralytic ileus, Elgar et al. concluded that each additional day of hospitalization increased the odds of mortality in nonoperative adult and elderly patients by 7.6% and 5.8%, respectively.[28] Similarly, Patel et al. stated that in a study of emergently admitted patients with umbilical hernia, in the adult nonoperation group, each additional day of hospitalization increased the mortality odds by 7.7%.[34] Finally, in a study that compared risk factors of mortality in emergently admitted adult and geriatric patients with the diagnosis of gastroparesis, Hirani et al. found that every additional day of hospitalization increased the odds of mortality by 12% and 10%, respectively.[36] Similar associations have been described in studies that investigated risk factors of mortality in intestinal fistulas patients.

Wu et al. found that enterocutaneous fistulas patients that were categorized as

Table IV
Backward multivariable logistic regression analysis to evaluate the associations between mortality and different factors in emergency admitted adult and elderly patients with the diagnosis of intestinal fistulas, excluding rectum and anus (NIS 2004–2014)—mortality was the dependent variable

		Adults (18-64 years)		Elderly (65+ years)	
		OR (95% CI)	p-value	OR (95% CI)	p-value
Age, Years		Removed via Backward Elimination		1.07 (1.03, 1.10)	<0.001
Sex, Female				1.58 (0.97, 2.58)	0.1
Days to the First Procedure				1.03 (1.01, 1.04)	0.003
Comorbidities	**Coagulopathy**	4.98 (2.50, 9.93)	<0.001	4.81 (2.52, 9.17)	<0.001
	Fluid/Electrolyte Disorders	2.24 (1.24, 4.03)	0.007	2.10 (1.34, 3.29)	0.001
	Renal Failure	2.95 (1.50, 5.79)	0.002	2.23 (1.33, 3.75)	0.002
	AIDS	7.26 (0.77, 68.29)	0.1	Removed via Backward Elimination	
	Metastatic Cancer	3.01 (1.44, 6.29)	0.003		
	Valvular Disease	3.47 (1.01, 11.94)	0.048	1.66 (0.98, 2.81)	0.1
	Congestive Heart Failure	Removed via Backward Elimination		3.99 (1.13, 14.01)	0.031
	Paralysis				

Bold indicates result is statistically significant

bleeders had prolonged intensive care unit and hospital length of stays compared to the non-bleeders, which was one factor that determined a worse outcome.[5] Of the 67 (33%) enterocutaneous fistulas patients that were categorized as bleeders, hospital length of stay was 30.7 ± 27.3 days in the bleeder group compared to 24.3 ± 17.6 days in the non-bleeder group, which was a statistically significant difference.[5] Marfil-Garza et al. concluded, in an 18-year retrospective study of hospitalizations in a Mexican tertiary healthcare center, that complex abdominal diseases like intestinal fistulas had one of the greatest risks for prolonged hospital length of stay with an odds ratio of 2.57 (95% CI: 1.98–3.32, p<0.001).[41] In this study, prolonged hospital length of stay was defined as greater than 34 days.[41]

Being able to have standardized care for patients with intestinal fistulas should be a goal of all tertiary hospitals in order to improve patient outcomes, reduce readmissions, and diminish healthcare expenditure. However, standardization of care for enterocutaneous fistulas patients has not occurred in a majority of tertiary hospitals.[42] Kugler et al. performed a retrospective analysis of outcomes in a large hospital after the implementation of a four-stage protocol for managing enterocutaneous fistulas patients.[42] This protocol focused on correcting intravascular volume deficits, improving wound management, controlling fistulas output, addressing comorbidities, and maintaining regular nutritional support, while also addressing patient mobility and social constructs.[42] Compared to the pre-cohort (patients treated prior to the protocol), the post-cohort (patients treated after the protocol) enterocutaneous fistulas patients demonstrated high spontaneous closure rates with a decreased hospital length of stay (37 days in the pre-cohort vs. 17 days in the post-cohort) and a lower morbidity and mortality.[42] Additionally, post-cohort patients had a higher spontaneous closure rate (84% vs. 16% in the pre-cohort) and a lower percentage of patients required operative closure (16% vs. 60% in the pre-cohort).[42] Other areas that need to be addressed to reduce hospital length of stay are coordinating communication between providers and home care agencies, early identification of insurance needs to allow for adequate time for approval, and aligning family and patient expectations with those of healthcare providers.[42] Froiio et al. conducted a similar study with 1061 colovesical fistulas patients and found that having a standardized perioperative care plan in place can improve clinical outcomes, reduce hospital length of stay, and decrease the duration of Foley catheterization.[43] These studies validate the necessity of having stringent intestinal fistulas treatment protocols, which allows for a safe and timely discharge by addressing the patients' clinical, social, and financial needs.[42]

A large proportion of adverse outcomes from longer hospital length of stay is due to nosocomial infections.[28,44,45] Jia et al. reported in a study across 68 Chinese hospitals that nosocomial infections caused an increase in hospital length of stay by 10.4 days.[44] In a similar analysis, hospital length of stay longer than seven days was found to be highly correlated with healthcare-associated infections in low- and middle-income countries.[46] Nosocomial infections not only impact the patient's health and quality of life, but they also bring economic burden to the patients and the healthcare system.[44] These findings emphasize the beneficial effects of utilizing hospital length of stay as a prognostic tool.[27–29,31,45,47]

The impact of days to the first procedure on mortality risk

Our analysis shows that elderly patients had an increased risk of mortality with a greater length of time to the first procedure after fistulas development. Some studies conclude that prolonged delays to intestinal fistulas corrective surgery can result in increased risk of fluid and electrolyte depletion, sepsis, malnutrition, and death, which confirm the results of our research.[48–50] However, other studies conclude that improved outcomes result from delaying corrective surgery, which challenges the results of our research.[51–53] Due to these conflicting results, being able to determine the optimal time for surgical intervention has not been well-defined in the literature.[48] Before comparing our results to other published studies, its crucial to address the concept of spontaneous fistulas closure.

Spontaneous fistulas closure occurs without corrective surgery, and the rate of closure is higher for patients with fistulas from surgical causes, low output fistulas, and those with fewer comorbidities and complications.[4] Spontaneous closure can be achieved through conservative management, which relies on maintaining optimal nutrition, fluid correction, wound care, and sepsis control over the course of 6–12 weeks.[53] However, the exact timeframe of conservative treatment should be based on the anatomic studies of the fistulas tract.[48] Acute postoperative gastrointestinal fistulas are more likely to close spontaneously than chronic gastric or pancreatic fistulas.[19] When spontaneous closure is not possible through conservative treatments, surgical closure is required for patients with higher output and more complex fistulas.[4,53]

Many studies have published findings that describe an increased risk of mortality for each additional day to operation in emergently admitted patients, using the same National Inpatient Sample database.[27,45,47,54–56] Levy et al. concluded that in operated adult and elderly patients that were emergently admitted with rectal or rectosigmoid junction malignancy, one day of increased time to surgery increased the odds of mortality by 4% and 5%, respectively.[27] Similarly, Idris et al. reported that in emergently admitted adult and elderly patients with acute gastric ulcers, for each additional day in delay to surgery, there was an increase in mortality odds by 13.5% and 10%, respectively.[54] Finally, Latifi et al. and Smiley et al. also described similar findings of increased risk of mortality when surgery is delayed for emergently admitted ventral hernia patients.[47,55]

Noori et al. concluded in a study of 23 postoperative enterocutaneous fistulas patients that delaying surgery and improving the patient's health status improved surgical outcomes by increasing closure rate, decreasing recurrence, and reducing mortality.[53] This points to the notion that increasing time to the first procedure reduces mortality risk, which is in direct opposition to our results. Surgical intervention was performed after an average period of 28 days (range, 18–42 days) from the diagnosis of the fistulas, and Noori et al. reported a mortality rate in the corrective surgery group of 17.3%.[53] It is important to note that this study found that a certain period of conservative treatment is always required in order to optimize the patient's general conditions and increase the chances for spontaneous closure.[53] These results can be explained by the fact that Noori et al. improved their patient's underlying conditions prior to operative correction, which maximized the chances of successful fistulas closure surgery and increased the time between fistulas diagnosis and procedure.[53] Dárdai et al. reported that in an 18-year review of 64 patients treated for postoperative enterocutaneous fistulas of the stomach, duodenum, jejunum, and ileum, timing of fistulas surgery had little impact on the fistulas closure rate.[51] This extensive review concluded that although the timing of the fistulas surgery was not strongly correlated with fistulas closure, better results were obtained when reconstructive surgery was deferred beyond six weeks from the fistulas onset.[51] When intraabdominal conditions are optimized, safe and definitive surgery can occur.[51] Similarly, Conter et al. concluded in a retrospective analysis of 51 patients with complex enterocutaneous fistulas that improved outcomes occurred when corrective surgery was deferred beyond the six week period.[52] Finally, Lloyd et al. also concluded that delaying corrective surgery in enterocutaneous fistulas patients allows time for metabolic and nutritional deficiencies to be corrected.[57]

Lee et al. and Visschers et al. supported the results of our analysis, and they found that prolonged delays in enterocutaneous fistulas corrective surgery can result in an increased risk of fluid and electrolyte depletion, sepsis, and malnutrition.[48,49] These complications are strong risk factors for mortality because these patients will be reliant on parenteral nutrition to fulfill their nutritional demands, which can lead to further adverse effects like catheter-site infections and metabolic abnormalities.[7,58] However, in order to be eligible for surgery, patients need to have their septic foci adequately treated nutritional demands met, while meeting certain subjective criteria for good clinical condition.[49] Carlson et al. also found that in the surgical management of intestinal fistulas patients that develop intestinal failure, surgical treatment should not only be timely and effective, but also aimed at preventing secondary damage to the small intestine in order to minimize the risk of short bowel syndrome.[50] When managing intestinal fistulas patients, an equilibrium has to be maintained where the patient's baseline conditions are optimized in order to improve outcomes for corrective surgery. However, too much time between fistulas onset and surgery can increase the chances of complications and mortality.[48–50,54–56] These results highlight the point that the therapeutic approach cannot be uniform in all types of postoperative intestinal fistulas, and the timing of definitive surgery should be individualized according to patient characteristics.[48,59] These conflicting recommendations can be explained by the complexity and variability in how intestinal fistulas patients present.

The impact of age on mortality risk

Additionally, we have demonstrated that age is a major predictor of mortality in emergently admitted elderly patients with the diagnosis of fistulas of the intestine, excluding the rectum and anus. Our results are supported by many other studies that report the older the patient, the lower their likelihood of survival.[2,4,6–8,10–12,36,55,56,60] This association has been demonstrated multiple times in similar studies that also utilized data from the National Inpatient Sample.[30,33,36,37,55,56] Lee et al. concluded, in a study of 27,688 emergently admitted patients with rhabdomyolysis, that for every additional year of age, odds of mortality increase by 3%.[30] Furthermore, in a study of 7,214 elderly patients with ruptured abdominal aortic aneurysms, Lobao et al. found that each additional year of age caused higher mortality odds of 4%.[33] Likewise, Newbury et al. came to a similar conclusion that age was a significant independent predictor of mortality in nonelderly patients admitted with bleeding gastritis.[37] Similar connections between increased age and mortality have also been studied in intestinal fistulas patients.

In a study of 50 patients that presented with aortoenteric fistulas repair between 1995–2014, Chopra et al. reported that advanced age was an independent predictor of mortality on multivariable regression models (HR 1.07; 95% CI: 1.01–1.13, p=0.01).[6] Increased age in emergently admitted patients is associated with worsening frailty, which is significantly linked to poorer patient outcomes like mortality.[61] Likewise, Dárdai et al. concluded, in 71 cases of enterocutaneous fistulas over an 18-year study, that patients over 65 years old had a rise in mortality rate compared to younger patients (69% in patients over 65 vs. 27% in younger patients).[51] Some authors have

stated specific age cutoffs that are associated with increased mortality—Martinez et al. and de Vries et al. reported that intestinal fistulas patients above the age of 55 were at a statistically significant risk for mortality.[7,8] Similarly, Wercka et al. found that postoperative abdominal fistulas patients over the age of 60 were an independent predictor of mortality.[14] Other authors like Campos et al. have reported mortality rates for different age groups—out of 188 patients with gastrointestinal fistulas, 61% of patients above the age of 50 died, while 48% of patients below 50 died.[19] However, this was not a statistically significant result.[19]

Mawdsley et al. analyzed predictive factors for healing and mortality in 277 patients with enterocutaneous fistulas and reported that age was independently associated with fistulas-related mortality.[12] In this study, older patients had higher fistulas output, which were linked to a greater risk of mortality.[12] Most of the deaths in the older patients were due to fistulas-related sepsis.[12] Because higher output fistulas are associated with reduced fistulas healing, it is the failure of fistulas healing that leads to an increased chance of an episode of fistulas-related sepsis.[12] Additionally, Mawdsley et al. found that older patients had lower serum albumin concentrations and were more likely to be deemed as poor operative candidates.[12] Chances of fistulas resolution decreases when patients do not have the option for corrective surgery. There are some studies, however, that conclude that the age of the intestinal fistulas patient does not hold predictive value in determining mortality risk.[11,62] Supe et al. reported that age had no significant effect on healing or mortality in intestinal fistulas patients.[11] Martínez-Ordaz et al. concluded that patients over the age of 70 with enterocutaneous fistulas have the same mortality rate that is reported in the overall population.[62] Because this study only included 19 patients, further research is necessary to verify these results.[62]

The impact of comorbidities on mortality risk

Our multivariable analysis showed an increased risk of mortality in both adult and elderly patients with the comorbidities of coagulopathy, fluid/electrolyte disorders, and renal failure. The final multivariable model for adults also showed a statistically significant increased risk of mortality in patients with metastatic cancer and valvular disease, which was not found in the elderly cohort. The comorbidity of paralysis was a statistically significant risk factor of mortality in the elderly cohort, but not in the adult cohort. Many previous studies have clearly demonstrated the links between these comorbidities and mortality. Coagulopathy was the comorbidity that was most strongly associated with mortality in adult and elderly intestinal fistulas patients in our study. Li et al. established that coagulopathic patients with a history of hemorrhage were at an increased risk for intra-abdominal bleeding in patients with enterocutaneous fistulas.[63] Intra-abdominal bleeding is a difficult complication to manage, and can easily exacerbate the intestinal fistulas, eventually leading to death.[63] To bring a patient with an intestinal fistulas back to normal coagulation status is a favorable prognosis that brings reduced complications in subsequent operations.[63] An inability to identify intestinal fistulas patients with coagulopathy can be a factor contributing to an increased mortality. Fluid and electrolyte disorders were comorbidities associated with mortality in both cohorts in the final multivariable regression model. Campos et al. concluded that one of the variables significant for death was fistulas output, which is intrinsically linked to fluid and electrolyte balances in intestinal fistulas patients.[4,5] Similarly, Wu et al. concluded that in a study of 162 patients with septic enteric fistulas, elevated serum sodium levels on days 0, 3, and 7 after admission were associated with increased risk of mortality.[64] Renal failure was another comorbidity that was associated with mortality in both cohorts in the final multivariable regression model. The comorbidity of renal failure is intrinsically linked to the previous significant finding of fluid and electrolyte abnormalities being a predictor of mortality because the kidneys are primarily responsible for the body's regulation of fluid and electrolyte balances.[65] The association that renal failure and chronic kidney disease are independent contributors of mortality in intestinal fistulas patients has been clearly established in previous research.[2,5–7,10,12] Metastatic cancer was another significant predictor of mortality in the adult cohort in the multivariable regression model. In cancer patients, metastasis is responsible for up to 90% of cancer-associated mortality.[66] Having this comorbidity with an existing intestinal fistulas significantly impacts mortality rates in emergently admitted patients. Valvular disease was the final significant predictor of mortality in the adult cohort in the final multivariable regression model. In a large population-based study of adults who were assessed by clinically indicated echocardiography, the adjusted mortality risk ratio associated with valvular disease was 1.75.[67] This significant increase in mortality risk is due to volume and pressure overload, which negatively impacts the recovery period and physiologic stability in patients with intestinal fistulas. Paralysis was the last significant predictor of mortality in the elderly cohort in the final multivariable regression model. The comorbidity of paralysis increases a patient's risk of acquiring pneumonia, septicemia, and pulmonary emboli, while also impacting a patient's life expectancy.[68] These complications can exacerbate the underlying diagnosis of intestinal fistulas, which prevents adequate healing after emergent admissions.

Strengths of the study

The primary strengths of this study relate to the large National Inpatient Sample database representing patient populations from a diverse spectrum of hospitals and geographic locations. This analysis was recorded during a 10-year period in the United States during 2004–2014. The purpose of these data was to improve healthcare through research by analyzing broad combinations of disease conditions, treatments, and outcomes in a large sample size over a 10-year period. The large patient population enabled us to identify the predictors of mortality associated with patients emergently admitted with intestinal fistulas. Because of this, our results are likely to be generalizable across a broad range of locations and healthcare settings. The sample size was large enough for accurate analysis with each statistical method. Previous studies focus on smaller sample sizes of the population over a smaller geographic region in a shorter period of time. Understanding various trajectories in morbidity and mortality is critical for guiding long-term therapy and patient optimization. This study serves to fill a gap in the literature on the demographics of elderly and adult patients suffering from intestinal fistulas in addition to their individual hospital course, disease management, and outcome of their care.

Limitations of the study

Utilizing the National Inpatient Sample database has led to some limitations in this study. This database does not contain information regarding the severity of the intestinal fistulas, etiology, pharmaceutical management, invasive diagnostic procedure protocols, operative techniques utilized, and severity of comorbidities. Further stratification of invasive diagnostic procedures, time to operation, and condition severity may allow for more accurate interpretations of the data. Because this was a retrospective study that utilizes an administrative dataset, there are certain variables that cannot be obtained, which would help in contextualizing the results. Our study does not include information regarding the types, cause, and severity of intestinal fistulas. Also, it does not include the length of time of fistulas before they require emergency admission (many of these patients are often in and out of hospitals with nutritional-related complication). Future research involving specific types of intestinal fistulas, interventional approaches, and severity of comorbidities could further shed light on this topic. Moreover, it would be very important that the National Inpatient Sample contained all additional datapoints suggested so that future studies can be more useful for researchers and clinicians.

CONCLUSION

In conclusion, increased age and increased days to operation were risk factors for in-hospital mortality in the elderly population undergoing emergent admission for fistula of the intestine, excluding the rectum and anus. Additionally, multiple comorbidities were risk factors for in-hospital mortality in both adult and elderly populations emergently admitted for intestinal fistulas. While the heterogenous nature of intestinal fistulas makes it challenging to conclude the presence of a single prognostic factor that increases the risk of mortality, various associations between patient demographics, hospital course, comorbidities, and mortality can be established. The information drawn from this study could be used to help physicians identify risk factors within their patients, which can optimize patient selection and assist them in managing the higher-risk patients. Further research is needed to elucidate how to alleviate some of these risk factors and the associations that can exist between certain risk factors and mortality. STI

AUTHORS' DISCLOSURES

The authors have no conflicts of interest to disclose.

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