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Influence of prior appendectomy and cholecystectomy on *Clostridioides difficile* infection recurrence and mortality

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ABSTRACT

Background: Remote appendectomy was linked to increased incidence of *Clostridioides difficile* infection (CDI). We evaluated the effect of absence of vermiform appendix and/or gallbladder on recurrence rate and severity of CDI.

Methods: We assessed a systemwide patient cohort diagnosed with initial CDI in 2014 (n = 250). The primary outcome was recurrence.

Results: Appendix and gallbladder were absent among 47 and 64 patients, respectively. CDI recurrence rate was similar among patients without and with appendix (24/47, 51.1% versus 90/203 patients, 44.3%; p = 0.404) and similar among patients without and with gallbladder (29/64 patients, 45.3% versus 85/186 patients, 45.7%; p = 0.957). Mortality was similar between appendectomy versus appendix *in situ* patients (3/47, 6.4% versus 9/203, 4.4%; p = 0.573), but higher mortality rate was seen among those without gallbladder (7/64 patients with prior cholecystectomy, 10.9% versus 5/186 patients with intact gallbladder, 2.7%; p = 0.008).

Conclusion: Clostridioides difficile recurrence rate is not affected by remote appendectomy or cholecystectomy. Patients with prior cholecystectomy experience higher mortality rates associated with their CDI.

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Background

Clostridioides difficile infection (CDI) has emerged as the most burdensome infection contributing to both suffering and healthcare expenditure.[1–3] Approximately 30% of initial CDI recur based on historical data, but increasing incidence of multiple recurrent CDI has been noted (Ma 2017). Risk factors for recurrence remain poorly defined, but loss of vermiform appendix has been cited by some as a risk factor for contracting CDI or its more severe course.[4–6] No prior data are published on possible interaction of post-cholecystectomy anatomy with risk of CDI recurrence.

Therefore, in context of increasing CDI burden coupled with high prevalence of appendectomy and/or cholecystectomy we evaluated the relationship of CDI recurrence and surgically-mediated absence of vermiform appendix and/or gallbladder. Secondary objective was to evaluate the influence of reported comorbidities, core skeletal muscle mass and other clinical factors on recurrence and death from the CDI.[7,8]

Methods

CDI was defined as the occurrence of diarrhea (≥3 unformed stools in 24 h) and presence of toxigenic *C. difficile* based on PCR toxin assay in absence of other obvious causes. Such confirmed CDI cases in our metropolitan healthcare system (outpatient and 750-bed inpatient facility) were reviewed over the course of one year (2014). Recurrence was defined as diarrhea recurrence within 12 months after the initial treatment course of at least 10 days of CDI-directed antimicrobials was completed. Cases with persistent or new diarrhea within 14 days of the initial diagnosis were considered a persistent CDI, and not as a recurrent disease. Absence of appendix was established by chart review and computed tomography (CT) imaging review if available. Patients who reported prior

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appendectomy, ileocolectomy, right colectomy, or total colectomy were considered to have appendix absent, while all others were considered to have appendix *in situ*. Similar procedure was performed to establish presence of gallbladder or history of post-cholecystectomy.

Demographic and clinical characteristics were established by chart review. Comorbidities were extracted and a Seattle Comorbidity Index was calculated as reported previously.[9] Body mass index (BMI) was defined as body weight (in kg)/height^2 (in m). Cross-sectional areas of the left and right psoas muscles at the level of the fourth lumbar vertebra were determined manually using Aquarius workstation on CT within 1 week of CDI diagnosis. Core skeletal mass was defined as total psoas area (TPA) normalized for height (TPA mm^2/m^2).[7] Based on our prior experience we evaluated a novel simplified method of psoas muscle cross-sectional area by measuring anterior-posterior (AP) and lateral diameter (LL) of each psoas muscle at the same level and calculated its surface estimate by equation of ellipse surface $Area = \pi * \frac{AP}{2} * \frac{LL}{2}$. We then performed pairwise correlation and linear regression between a formal TPA measurement on Aquarius workstation and the simplified measurement.

Statistical analysis

Data are provided as mean, median, and standard deviation for continuous variables. Missing data were not imputed but rather declared in Tables. The impact of core skeletal mass was evaluated as a continuous variable. Stepwise logistic regression models (removal probability $p < 0.2$) were built using all variables with $p < 0.4$ on univariate testing plus age, gender and indicator variables on presence of gallbladder and vermiform appendix. Post-estimation using Hosmer-Lemeshow test was used. Overall survival was evaluated using the Kaplan–Meier method. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata 15 (Stata Corp, College Station, TX, USA).

Results

There were 250 patients with average age 65.4 ± 20.1 years. There were no statistical differences between those experiencing recurrence or in-hospital mortality in age, Seattle comorbidity index, core skeletal muscle mass, smoking status, presence of active malignancy, history of coronary artery disease, heart failure, diabetes mellitus, chronic renal insufficiency or presence/absence of vermiform appendix (Table 1).

One hundred and thirty-six (54.4%) patients experienced a single episode of CDI, whereas 114 (45.6%) experienced at least one recurrence with the first recurrence on average 38.4 ± 19.6 days (median 34 days) after diagnosis of the initial episode (Fig. 1). Twelve patients died (4.8%) and an additional 3 were sent to hospice care (all 3 experienced clinical control of CDI and hospice was indicated due to unrelated terminal illness). All deaths occurred among hospitalized patients, who were older as compared to outpatients (69.2 ± 16.8 versus 59.7 ± 23.3 years, $p = 0.001$). Fecal microbiota transfer therapy was used in 6 patients (1 with the initial diagnosis of CDI and 5 cases of recurrent CDI). Antibiotic treatment was then contemporaneous with metronidazole ($n = 124$), oral vancomycin ($n = 65$), fidaxomicin ($n = 2$), and the rest with unknown initial therapy. There were no differences observed on recurrent CDI ($p = 0.546$) or deaths ($p = 0.310$) based on initial therapy used in this study population. Two patients required emergency total colectomy for their fulminant CDI: one had prior appendectomy and one in-situ appendix ($p = 0.384$), and similarly one had in-situ gallbladder and the other was after cholecystectomy ($p = 0.559$).

Vermiform appendix was missing among 47 patients and prior cholecystectomy was recorded among 64 patients. Of these patients 21 had neither appendix nor their gallbladder based on their prior surgical history (Table 1). Hospitalization was more common among patients without appendix (38 of 151 admitted patients, 25.1% versus 9 of 99 outpatients, 9.1%; $p = 0.001$). CDI recurrence rate was similar among patients without their appendix (24 of 47 patients, 51.1%) as compared to patients with appendix *in situ* (90 of 203 patients, 44.3%; $p = 0.04$). In hospital mortality was similar between appendectomy versus appendix *in situ* patients (3 of 47, 6.4% versus 9 of 203, 4.4%; $p = 0.573$). Interestingly, hospital length of stay (LOS) was shorter among alive, discharged patients without their appendix as compared to those hospitalized with their appendix *in situ* (6.2 ± 5.5 versus 9.5 ± 8.2 days; $p = 0.040$, Mann Whitney test).

Similarly, hospitalization was also more common among patients without their gallbladder (47 out of 151 admitted patients, 31.1% versus 17/99 outpatients, 17.1%; $p = 0.013$). CDI recurrence rate was similar among patients without their gallbladder (29 of 64 patients, 45.3%) as compared to patients with gallbladder *in situ* (85 of 186 patients, 45.7%; $p = 0.957$). Patients without their gallbladder experienced higher mortality rates associated with their CDI as compared to those with intact gallbladder (7 deaths out of 64 patients with prior cholecystectomy, 10.9% versus 5 deaths out of 186 patients with intact gallbladder, 2.7%; $p = 0.008$). Hospital LOS was nonsignificantly shorter among alive, discharged patients without their gallbladder as compared to those hospitalized with their gallbladder *in situ* (6.4 ± 5.1 versus 9.6 ± 8.4 days; $p = 0.067$, Mann Whitney test).

There were 21 patients without both their appendix and gallbladder, and 160 patients who had both organs at time of their CDI. Recurrent CDI was seen among 10 of 21 patient without both organs (47.6%) as compared to 71 of 160 patients with both organs *in situ* (44.4%; $p = 0.779$).

In-hospital mortality was modelled using stepwise logistic regression and identified intact gallbladder as protective against in-hospital mortality (Table 2, Fig. 2 and Fig. 3). Comorbidities, gender, age, and core skeletal muscle mass were not predictive of in-hospital death based on univariate and multivariate testing (Table 1). Direct measurement of total psoas area based on manual outline correlated tightly with estimate provided by measuring anterior-posterior and lateral diameters ($n = 100$; correlation coefficient $r = 0.942$, $p < 0.001$).

Patients with recurrent CDI were of lighter weight and lower BMI in univariate analysis (Table 1). Multivariate logistic stepwise regression could not identify any predictors of CDI recurrence using a pre-defined method. However, when predicting multiply recurrent CDI patients (≥2 recurrences) multivariate stepwise procedure retained renal insufficiency (defines as serum creatinine ≥2.0 mg/L) as a predictor of multiply recurrent CDI (OR = 3.697, 95% confidence interval 1.520–8.993, $p = 0.004$). Status of vermiform appendix and gallbladder were not predictive of multiply recurrent CDI.

Discussion

Clostridioides difficile infection (CDI) may have a variable course, yet it emerged as enteric pathogen worldwide.[2,3] There were some 500,000 infections related to CDI reported in 2011 with 29,000 deaths in the USA alone.[2] We investigated the impact of prior appendectomy and prior cholecystectomy on recurrence rate of CDI and its mortality in our cohort of patients prior to a widespread introduction of fecal microbiota transfer.

Both cholecystectomy and appendectomy are associated with a miniscule risk of immediate post-procedural CDI, 0.4% and 0.2%

Table 1
Demographic and clinical characteristics of the cohort. BMI – body mass index, sTPA – standardized total psoas area in mm^2/m^2. AMI – acute myocardial infarction, COPD – chronic obstructive pulmonary disease. qSOFA – Quick sequential organ failure assessment score. CDI – *Clostridioides difficile* infection.

	Total	Non-recurrent	≥1 recurrence	p	Survivor	Non-survivors	p
N	250	136	114	N/A	238	12	N/A
Age (years)	65.4 ± 20.1 (67.5)	65.7 ± 20.4 (69)	65.1 ± 19.8 (67.0)	0.662	65.2 ± 20.3 (67)	70.6 ± 17.1 (77.5)	0.405
Female gender	165 (66.0%)	89 (65.4%)	76 (66.7%)	0.832	158 (66.4%)	7 (58.3%)	0.566
Weight (kg)	78.0 ± 23.2 (72.4)	79.7 ± 22.6 (79.0)	76.1 ± 24.3 (69.0)	0.028	77.8 ± 23.2 (72)	81.7 ± 24.2 (83)	0.323
BMI (kg/m^2)	28.5 ± 8.4 (26.5)	29.1 ± 7.8 (27.2)	27.9 ± 9.1 (25.9)	0.058	28.5 ± 8.4 (26.4)	28.7 ± 7.9 (28.1)	0.604
Albumin (g/L)	3.4 ± 0.7 (3.5)	3.4 ± 0.7 (3.7)	3.3 ± 0.7 (3.4)	0.336	3.4 ± 0.7 (3.6)	2.6 ± 0.7 (2.6)	<0.001
sTPA (mm/m^2)	645 ± 222 (617)	652 ± 226 (625)	638 ± 220 (599)	0.715	649 ± 221 (612)	587 ± 242 (633)	0.623
Seattle comorbidity index	6.6±4.2[6]	6.7±4.2[6]	6.5±4.1[6]	0.828	6.5±4.2[6]	7.75±3.5[8]	0.367
Appendix absent	47 (18.8%)	23 (16.9%)	24 (21.1%)	0.404	44 (93.6%)	3 (6.4%)	0.573
Gallbladder absent	64 (25.6%)	35 (25.7%)	29 (25.4%)	0.957	57 (89.1%)	7 (10.9%)	0.008
Smoking status							
Never a smoker	131 (59.8%)	74 (63.2%)	57 (55.9%)	0.426	124 (59.9%)	7 (58.3%)	0.993
Former smoker	36 (16.4%)	16 (13.7%)	20 (19.6%)		34 (16.4%)	2 (16.7%)	
Current smoker	52 (23.7%)	27 (23.1%)	25 (24.5%)		49 (23.7%)	3 (25.0%)	
Missing data	31	19	12		31	–	
History of AMI	28 (12.6%)	16 (13.5%)	12 (11.4%)	0.632	27 (12.8%)	1 (12.6%)	1.000
Missing data	27	18	9		27	–	
Heart failure history	36 (15.9%)	17 (14.2%)	19 (17.9%)	0.441	35 (16.4%)	1 (8.3%)	0.696
Missing data	24	16	8		24	–	
Active malignancy	20 (9.0%)	12 (10.3%)	8 (7.6%)	0.493	18 (8.6%)	2 (16.7%)	0.341
Missing data	28	19	9		28	–	
COPD	36 (16.1%)	19 (15.9%)	17 (16.2%)	0.964	31 (14.6%)	5 (41.7%)	0.028
Missing data	26	17	9		26	–	
Diabetes mellitus	69 (30.8%)	37 (31.1%)	32 (30.5%)	0.921	64 (30.2%)	5 (41.7%)	0.402
Missing data	26	17	9		26	–	
Chronic renal insufficiency (Creat≥2.0)	68 (27.2%)	40 (29.4%)	28 (24.5%)	0.391	66 (27.7%)	2 (16.7%)	0.521
					–	–	
Pre-CDI acid suppression	135 (60.5%)	75 (63.5%)	60 (57.1%)	0.328	124 (58.8%)	11 (8.2%)	0.031
Missing data	27	18	9		27	–	
Initial qSOFA ≥2	22 (8.8%)	13 (9.6%)	9 (7.9%)	0.412	17 (8.5%)	5 (41.7%)	0.004

respectively.[3] Both operations, however, change gastrointestinal tract anatomy and were implicated in protection from or promotion of CDI.[5,6,10]

As many as 12–50% of cases suffer from recurrence after its initial treatment,[2,11] a figure even higher in some studies including ours. Multiply recurrent CDI (≥2 recurrences) increased by 42% in the first decade after 2000.[12] The disease increasingly takes a severe course and is associated with substantial morbidity and mortality. Prior antibiotics exposure, use of proton pump inhibitors, and others have been identified as risk factors, yet most patients with risk factors do not develop CDI.[1,2] Therefore, further understanding of risk factors for severe clinical course, organ failure, CDI recurrence, and mortality are needed.

Existing literature shows conflicting evidence on role of prior appendectomy on CDI. Appendectomy was found to increase risk of CDI reinfection[5] and was associated with a more severe clinical course including colectomy-necessitating fulminant CDI.[4,6] We found no effect of appendectomy status on recurrence of CDI in this study, a finding similar to few others.[13–15] Microbial content of vermiform appendix appear to lack *Clostridioides* species and is more diverse than that of gut microbiome.[16] In light of the present study and prior evidence we do not believe prior appendectomy is a risk factor for recurrent CDI, and consequently appendiceal preservation does not seem justified from this perspective despite availability of non-operative treatment for uncomplicated appendicitis.[17]

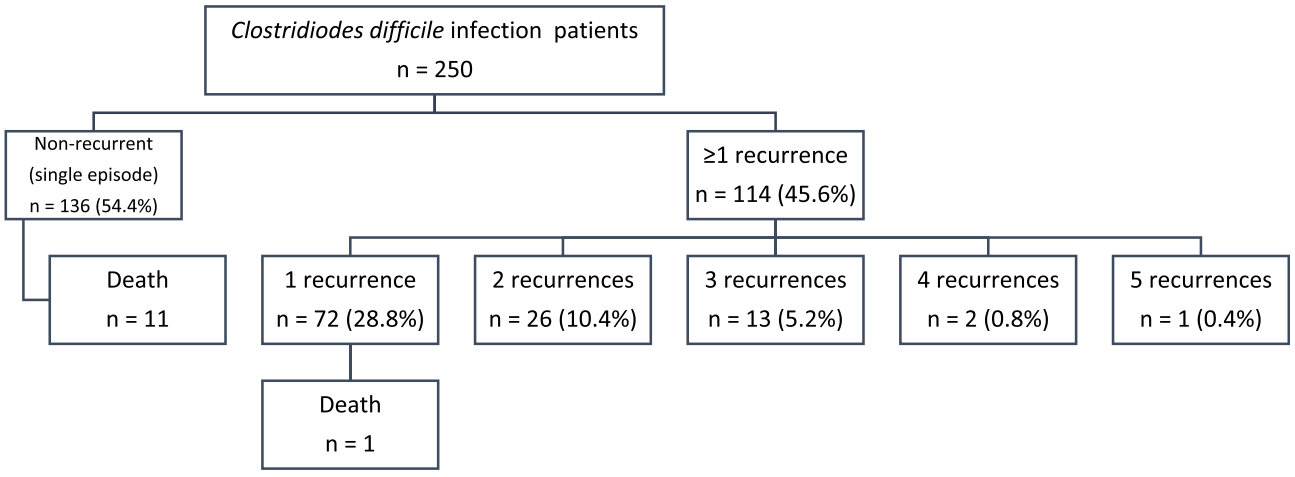

Fig. 1. *C. difficile* infection outcome in the study population.

Table 2
Logistic regression for in-hospital mortality among *Clostridioides difficile* patients. All factors significant in univariate analysis were entered into this multivariate model, plus both factors of interest (status of appendix and gallbladder). Overall model $p < 0.001$, Pseudo R2 28.4%. The model is consistent with data (Hosmer-Lemeshow $p = 0.238$). Age, gender, BMI, pre-existing comorbidities and acid suppression were excluded by stepwise procedure.

	OR	95% confidence interval for OR	p
Gallbladder *in situ* (baseline: prior cholecystectomy)	0.228	0.056–0.923	0.038
Albumin (per g/L)	0.197	0.070–0.557	0.002
qSOFA ≥2	8.063	1.845–35.224	0.006

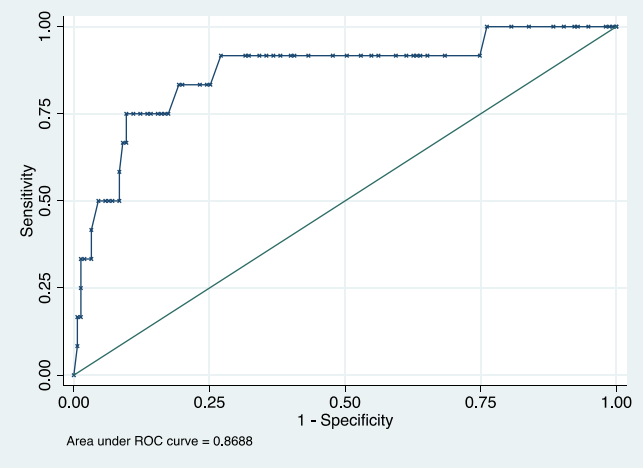

Fig. 2. Receiver operator curve for the logistic regression predicting death in Table 2 above. AUCROC = 0.868.

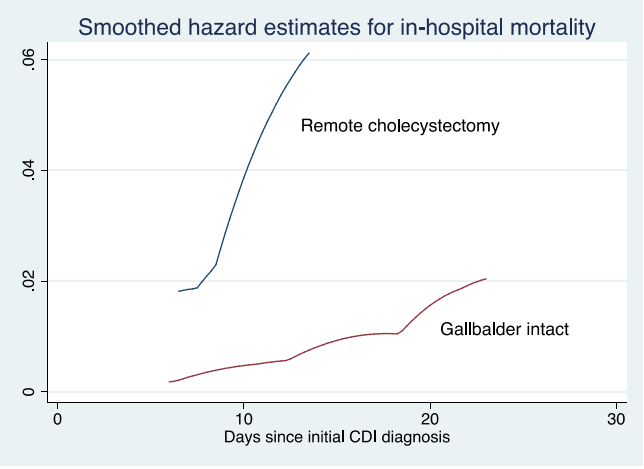

Fig. 3. Smoothed hazard estimates for in-hospital mortality based on presence or absence of gallbladder.

Fewer reports are available on the relationship of remote cholecystectomy and CDI, despite extensive knowledge that sporulation and germination are regulated by bile acids.[11,18,19] Gallbladder is intimately related to enterohepatic circulation of bile acids and their recirculation increases after cholecystectomy several fold.[20] A single prior study reported higher colonization rates by *Clostridioides difficile* among those with cholecystectomy.[10] Microbiota profile and bile acid content of normal, CDI patients, and CDI patients after fecal microbiota transplantation differ significantly.[19] In theory, cholecystectomy may lead to substantial changes in outcome of CDI, including recurrence and progression to severe CDI. Similar to one prior study we did not identify higher risk of CDI recurrence among those with prior cholecystectomy.[21] Whether severity of CDI is influenced by pre-existing cholecystectomy has not been previously studied to our knowledge, therefore our finding of increased risk of death among patients with prior cholecystectomy requires further scrutiny.

CDI recurrence risk and risk of death were not predicted by comorbidities or skeletal muscle mass. Many other studies did not identify comorbidities as recurrence risk factors, perhaps with notable exception of renal insufficiency and/or chronic liver disease.[11,21] Skeletal mass is inversely related to sarcopenia, a recognized predictor of frailty and lowered resilience and increased mortality.[7,8] While sarcopenia has been associated with increased mortality in several conditions, we have identified no relationship with rate of recurrence or death from CDI in this study population.

The present study features several limitations, including retrospective character and conduct prior to recent CDI treatment change favoring fidaxomicin and increased acceptance of fecal microbiota transfer.[22] We have not distinguished between CDI relapse and reinfection with different subtype of toxigenic *Clostridioides difficile*. While these factors may have influences on presented results, at present we do not see any mechanistic explanation of such effect.

Prior appendectomy (or presence of intact appendix) did not influence CDI recurrence rate or mortality in our study population. Others have found that prior appendectomy may be associated with increased risk of fulminant CDI.[4,6] Interestingly, appendectomy carries protective risk against development of multiple seemingly unrelated diseases, including lesser risk of ulcerative colitis[23] and Parkinson's disease.[24] The absence of gallbladder was not associated with altered recurrence rate. Post-cholecystectomy state, however, was associated with increased mortality risk in both univariate and multivariate models, suggesting possible role of gallbladder in prevention of fulminant or fatal course of CDI.

Conclusions

Prior appendectomy and/or cholecystectomy do not affect recurrence rate of *Clostridioides difficile* infection. Patients with prior cholecystectomy experience higher mortality rates associated with their CDI.

Declaration of competing interest

Primary author – Jan Franko – declared on behalf of all authors that no one have any conflict of interest, financial or otherwise, associated with the submitted paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.10.038.

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